assays in the hypothesized surfactant AOP, these results may be interpreted to indicate that the new chemical substance has "lower" toxicity than the comparator substance. In such cases, then the modified POD$_{HEC}$ for the comparator substancenew chemical substance should be used for quantifying the MOE. If risks are identified with the modified POD$_{HEC}$, then stop at Tier II. However, if it is not possible to calculate a modified POD$_{HEC}$, then the comparator substance POD$_{HEC}$ should be used for risk assessment. Otherwise, proceed to Tier III.

Third, if the results obtained are equivocal (i.e., they do not fit within either of the first two scenarios) (e.g., positive findings, but not findings that support a positive/negative result in one or more of the assays), then proceed to Tier III because the data are too uncertain to make a reasoned evaluation on the potential health risks, following potential inhalation exposures.

**Commented [SM88]:** This section still need some rework: I understand that you have always to compare to the reference / comparator substance. Always MOE can be calculated and to compared to benchmark MOE… this three cases are always given. If you choose a "safe" comparator und your are equal or lower than you "safe" as well right? We should mention this in each section The fourth case is that the test systems itself may deliver no consistent (like always same trend to comparator) results so that you can not use this approach of transfer, I guess this is mentioned with third case here. For this you cannot calculate an MOE that's why you have to go on in testing.. maybe we can orientate on the fact if you can calculate an MoE?

## Tier III – Human Airway Models/PCLS Assay

Several testing options are available for evaluating OLEs in the surfactant AOP. The test system employed should focus on evaluating effects in the respiratory tract at the predicted sites of deposition (e.g., TB and/or PU regions) using RDDR or MPPD modeling. A justification for using a particular system(s) should be provided and may be discussed with EPA as part of a pre-notice consultation. AvailableRepresentative test systems include those listed in [ REF _Ref46931271 \h \* MERGEFORMAT ], but are not limited to, the following:

* EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells

[PAGE ]

- ~~MucilAir EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells~~

- ~~SmallAir™ 3-D constructs of primary human small airway epithelia reconstituted *in vitro*.~~

- ~~Precision-cut lung slice test *etc.* as described by Hess *et al.* (2016)~~ [ ADDIN EN.CITE ADDIN EN.CITE.DATA    ]

Based on the results of the 3D-construct and/or PCLS testing, IVIVE may be possible for developing a $POD_{HEC}$ for use with characterizing potential risks using the MOE approach. Though the occupational/consumer exposure estimates may be the same between Tiers II and III, the Tier III test results may offer the opportunity for refining the risk estimates. For example, the BMR used for calculating the $POD_{HEC}$ may be refined because the ALI-based exposure is more consistent with inhalation exposure in a human than the submerged culture exposures employed in Tier II [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2018</Year><RecNum>14811</RecNum><DisplayText>[97]</DisplayText><record><rec-number>14811</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045320">14811</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Issue Paper: Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-

title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>33, https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/bcgnd-1-epa_case_study.pdf</pages><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. Further, application of uncertainty factors for calculating the benchmark MOE may also be refined, if for example, human cultures are used, which may preclude the need for applying a $UF_A$.

If the Tier III test data are amenable for developing a $POD_{HEC}$, then the risk estimates should be reassessed. If no risks are identified under the conditions of use, then stop at Tier III. If risks are still identified under the conditions of use or if the Tier III test data are not amenable for developing a $POD_{HEC}$, then proceed to Tier IV.

**Tier IV – *In vivo* studies**

Strategic *in vivo* testing may be needed to inform the hazard and risk assessment of new chemical substances, particularly in those instances where a new chemical substance has unique properties that preclude a determination that one of the comparator substances in a subcategory analogues is appropriate for read-acrosshas representative toxicological properties to the new chemical substance, as well as in instances where the test data generated under Tiers II and III are not amenable for deriving modified $POD_{HECS}$. If *in vivo* testing is needed, a pre-notice consultation meeting with EPA is strongly encouraged prior to initiating any vertebrate animal testing. This point is especially important because TSCA section 4(h)(3) indicates that any

person developing information for submission under TSCA section 5 on a voluntary basis shall first attempt to develop the information by means of an alternative test method or strategy identified by EPA before conducting new vertebrate animal testing [ ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>14796</RecNum> <DisplayText>[80]</DisplayText><record><rec-number>14796</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041048">14796</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S.C.</author></authors></contributors><titles><title> Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-title></titles><periodical><full-title>United States Code (U.S.C.)</full-title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53 &amp;edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

The potential for surfactants to cause adverse effects on the respiratory tract are based on acute toxicity concerns, that is, interfering with epithelial lining fluid/pulmonary surfactant and/or disrupting cellular membranes and epithelial cytotoxicity. Since these effects may be captured using appropriate exposure concentrations in short-term inhalation studies, the following *in vivo* tests should be considered:

- Step 1: OECD Acute TG 403 [ ADDIN EN.CITE
  <EndNote><Cite><Author>OECD</Author><Year>2009</Year><RecNum>14827</Re
  cNum><DisplayText>[114]</DisplayText><record><rec-number>14827</rec-
  number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
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  Article">17</ref-
  type><contributors><authors><author>OECD</author></authors></contributors><titles
  ><title>Acute Inhalation Toxicity</title><secondary-title>OECD Guidelines for the
  Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD
  Guidelines for the Testing of Chemicals</full-title></periodical><pages>19,
  https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-
  tg403.pdf</pages><volume>403</volume><dates><year>2009</year></dates><urls></
  urls></record></Cite></EndNote>] (modified)** featuring rats exposed for 4 hours and
  observed for 2 weeks using aerosol exposure.

- Step 2: 5-Day inhalation study with a 14-day observation period** to address
  progression/resolution of effects. The OECD TG 412 [ ADDIN EN.CITE
  <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14828</Re
  cNum><DisplayText>[115]</DisplayText><record><rec-number>14828</rec-
  number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
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  Article">17</ref-
  type><contributors><authors><author>OECD</author></authors></contributors><titles

><title>28-day (subacute) inhalation toxicity study</title><secondary-title>OECD
Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-
title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>23,
https://doi.org/10.1787/9789264070783-
en</pages><volume>412</volume><dates><year>2018</year></dates><urls></urls></r
ecord></Cite></EndNote>] should be used, but the exposure duration should be 5 days.

**\*\*Modifications ~~(to discuss with EPA during study design)~~ to the above studies should be
discussed with EPA during a pre-notice consultation meeting and may include~~should consider are
e.g. (if measurable) including~~: pulmonary function testing (if measurable), analysis of BALF,
LDH release, complete histopathological analysis of the respiratory tract and blood oxygen
(pO$_2$) content. OECD TG 412 and OECD GD 39 [ ADDIN EN.CITE
<EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum>
<DisplayText>[106]</DisplayText><record><rec-number>14819</rec-number><foreign-
keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"
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type><contributors><authors><author>OECD</author></authors></contributors><titles><title
>Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment, No. 39
(Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the
Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology,
Organization for Economic Cooperation and Development</secondary-
title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals

**Commented [RJ89]:** This is not typically required in short term testing and therefore should be included here if one wants to gather valuable information on effects of surfactants.

**Commented [ST90R89]:** Agreed

**Commented [SK91]:** Rick: I don't think a separate satellite group is needed for recovery since the studies require holding all the animals for a 14 day observation period.

**Commented [HT92R91]:** Todd keith edited to remove satellite; OK?

**Commented [SM93]:** To my knowledge there is a special group needed for measureing blood oxygen and this is very tricky. Modification should be always consider carefully if they are possible and necessary at that stage. Maybe we can add "Modifications are e.g. .... to finally discuss during study design with EPA.

[PAGE ]

Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</full-title></periodical><pages>106, https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&amp;doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] should be consulted. Additionally, the sensory irritant potential can be measured using ASTM E 981 to determine reflex inhibition [ ADDIN EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>2001</Year><RecNum>14826</RecNum><DisplayText>[116]</DisplayText><record><rec-number>14826</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048712">14826</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Alarie, Y.</author><author>Nielsen, G.D.</author><author>Schaper, M.M.</author></authors><secondary-authors><author>Spengler, B.</author><author>Samet, J. M.</author><author>McCarthy, J.F.</author></secondary-authors></contributors><titles><title>Animal Bioassays for Evaluation of Indoor Air Quality</title><secondary-title>Indoor Air Quality Handbook</secondary-title></titles><pages>23.21-23.49.</pages><dates><year>2001</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill</publisher><urls></urls></record></Cite></EndNote>].

The results of the *in vivo* testing should be used for reassessing and recharacterizing the risks estimated using a surfactant analogue comparator chemical of the new chemical substance.

> **Commented [SM94]:** I think this is no longer needed? Instead I would mentioned that the results are used as POD and to calculate MOE? Or is the meaning now the other way around, sorry do not fully understand
>
> **Commented [ST95R94]:** Agreed

**CONCLUSIONS**

The overall objective of this investigation was to develop a chemical category for use in conducting inhalation risk assessment for new chemical surfactant substances under TSCA. This investigation developed physical-chemical properties, *i.e.*, the Surfactant Criteria, assessors can use for determining whether a new chemical substance can be considered a surfactant. Further, properties and characteristics are provided to divide the surfactant category into sub-categories for nonionic, anionic, and cationic surfactants, which is important from a toxicological perspective. A systematic literature search and review were conducted to identify data to define a surfactant category and ~~toxicological analogues~~substances from which ~~read-across could be performed~~PODs were identified from inhalation toxicity studies. To facilitate chemical comparisons, animal toxicity studies that could be used to derive PODs for risk assessments were identified for at least one ~~analogue comparator~~chemical substance for each sub-category and converted to HECs using established methods developed by EPA. Finally, a tiered-testing strategy is provided that focuses on integrating a variety of currently available NAMs using an AOP framework. Though the tiered-testing strategy may be aspirational for a variety of reasons (*e.g.*, evolving understanding of the representativeness of *in vitro* systems to *in vivo* systems, jurisdictional requirements for vertebrate animal testing, *etc.*), the use of this strategy will inform expanding the use the available data on surfactants and providing greater confidence in the use of non-vertebrate testing approaches for assessing the potential risks of new chemical substances. It also offers advantages to regulators, the regulated community, and consumers because integrating NAMs into a category testing approach not only supports EPA and TSCA goals of reducing and replacing vertebrate animal testing ~~and~~, but also it serves to encourage

development of mechanistic data to advance the understanding of the potential inhalation toxicity of surfactants, which will drive the development of newer and safer chemistries.

## ASSOCIATED CONTENT

**Supporting Information**

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. RDDR Modeling Outputs

## AUTHOR INFORMATION

**Corresponding Author**

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**Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

[PAGE ]

EPA sponsored the initial literature review through a government contract to SRC (68HERH19F0197 (TO#07)). The American Chemistry Council's TSCA Section 5 Testing Consortium sponsored an updated literature review by an independent third party.

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## Notes

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

Disclosures: TS, AMJ, KS, WI, and TRH are employed by the federal government. MPH, WK, AMK, SM, LJ, JLR, AT, and RT are employed by companies that manufacture, process, and/or use surfactants. RAB and SOS are employed by a company that represents companies that manufacture, process, and/or use surfactants. PDM and SDS work for a company that received contract funding from companies that manufacture, process, and/or use surfactants. MO and JM work for a company that receives contract funding from the federal government.

## ACKNOWLEDGMENT

Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).

## REFERENCES

[ ADDIN EN.REFLIST ]

| From: | Stephanie Snyder [stephanie.snyder@covestro.com] |
|---|---|
| Sent: | 7/31/2020 4:31:41 PM |
| To: | Stedeford, Todd [Stedeford.Todd@epa.gov]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Salazar, Keith [Salazar.Keith@epa.gov]; Henry, Tala [Henry.Tala@epa.gov] |
| Subject: | RE: revised draft for polymer lung overload + supporting information file |
| Attachments: | Draft manscript insoluble polymers and lung overload - 30 July 2020.ver.1.docx |

Hi Todd,

The lastest version with the edits we just made is attached.

Thanks,
Stephanie

**From:** Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
**Sent:** Thursday, July 30, 2020 7:07 PM
**To:** Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Stephanie Snyder; Tveit, Ann; Irwin, William; Salazar, Keith; Henry, Tala
**Subject:** revised draft for polymer lung overload + supporting information file
**Importance:** High

All,

Please find the attached, revised draft of the lung overload manuscript and the supporting information file for our call tomorrow. I kept all changes in track changes, so you can see the updates based on edits/comments received to date.

Thanks,


Todd

# Polymer Lung Overload Category: The Application of a New Approach ~~Methodologies~~ Methodology (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

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**ABSTRACT**

Poorly soluble and non-reactive high-molecular weight (HMW) polymers ($\geq$10,000 Daltons)

represent a generic category of substances that are extensively used in industrial and consumer

applications (*e.g.*, plastics). Under the 2016 amended Toxic Substances Control Act (TSCA),

HMW polymers may qualify for an exemption from the pre-notification requirements that exist

for polymeric, new chemical substances. However, for HMW polymers that do not meet the

exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental

Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload.

In the present evaluation, a systematic review of the literature was performed to identify studies

that would aid with defining key properties for determining whether respirable HMW polymers

may present an unreasonable risk to human health. These properties included: respirability,

reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for ~~several~~ a toxicological analogues that ~~can~~ may be used as a first step in risk assessments on these substances. Finally, a tiered-testing strategy was developed as a new approach method that maximizes the use of non-vertebrate testing (*i.e.*, NAMs) was developed that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

## INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21$^{st}$ Century Act was signed into law on June 22$^{nd}$, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1.  The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));

2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));

3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));

4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or

5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, "up-front" testing requirements (*e.g.*, the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA ), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><Dis

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0 CFR § 720.50 - Submission of test data and other data concerning the health and

environmental effects of a substance</title><secondary-title>Code of Federal

Regulations</secondary-title></titles><periodical><full-title>Code of Federal

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location>U.S.</pub-location><urls><related-

urls><url>https://www.law.cornell.edu/cfr/text/40/720.50</url></related-

urls></urls></record></Cite></EndNote>].


EPA's New Chemicals Program (NCP) has historically used various approaches to evaluate the

potential hazards of new chemical substances including the use of computational toxicology

models and analogue and category approaches to "read-across" from existing data to new

chemical substances for various requisite extrapolations. EPA's TSCA New Chemicals Program

(NCP) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on

specific chemical definitions and categorical boundaries that summarize the hazard concerns

(*e.g.*, human health or environmental toxicity) and recommend testing that may be conducted

prior to submitting a new chemical substance notification [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><Dis

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>T

SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</full-

title></periodical><pages>https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>201

0</year></dates><urls></urls></record></Cite></EndNote>].


Although the NCP Chemical Categories document provides transparency to the regulated

community on the potential concerns that EPA may have for hazards of specific chemistries or

physicochemical propertiesto the regulated community on the potential concerns that EPA may

have for hazards of specific chemistries or physical properties, the NCP Chemical Categories

were developed prior to the enactment of the amendments to TSCA, and therefore, do not reflect

new vertebrate testing reduction goals [ ADDIN EN.CITE

<EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>79</RecNum><Di

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&amp;edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cit

e><Cite><Author>Wheeler</Author><Year>2019</Year><RecNum>80</RecNum><record><

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keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Wheeler,

A.R.</author></authors></contributors><titles><title>Directive to Prioritize Effects to Reduce

Animal Testing</title><secondary-title>United States Environmental Protection

Agency</secondary-title></titles><periodical><full-title>United States Environmental

Protection Agency</full-title></periodical><pages>3,

https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-

231249.pdf</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndN

ote>]. For example, the testing strategy in the NCP Chemical Categories document for

respirable, poorly soluble particulates[1] includes ~~vertebrate animal testing, such as~~ a 90-day

subchronic inhalation toxicity study in rats with a 60-day recovery period [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><Dis

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[1] EPA identified particles as "respirable" to humans "if there are any particles $\leq 10$ μ[m] in diameter [not otherwise specified, e.g., physical or aerodynamic] in the material being handled by workers" and included "poorly soluble" compounds citing ILSI (2000) [56].

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Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</full-

title></periodical><pages>https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>201

0</year></dates><urls></urls></record></Cite></EndNote>]. Further, the NCP Chemical

Categories cover the defined boundaries defined thereinand therefore may not reflect

development ofinclude alternative chemistries that are intended to replace a chemical in the do

not fit within the current NCP Chemical Categories, even for chemicals that the alternative

chemistries are intended to replace (*e.g.*, the use of polymeric alternatives to replace monomeric

forms of existing chemical substances).

Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has also

developed exemption criteria for specific types of polymeric substances, based on its findings

that they "will not present an unreasonable risk of injury to human health or the environment

under terms of the exemption", for specific types of polymeric substances [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><Dis

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Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-

title>Federal Register</full-title></periodical><pages>16316-

16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dat

es><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria

are exempt from the new chemical substance notification requirements, although there are still

~~some requirements, including~~ annual reporting and recordkeeping requirements [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><Dis

playText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>4

0 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-

title></titles><periodical><full-title>Code of Federal Regulations</full-

title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><ye

ar>2020</year></dates><urls></urls></record></Cite></EndNote>].

EPA's polymer exemption established three polymer exemption types, designated as E1, E2, and E3. The general criteria for new chemical polymer substances meeting these exemption types for polymers are shown in [ REF _Ref46665925 \h \* MERGEFORMAT ].

**Table [ SEQ Table \* ARABIC ].** EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

| Exemption Type[a,b] | Number-average molecular weight (NAMW) | Oligomeric Material Criteria | Functional Groups (FGs)[c] and Functional Group Equivalent Weight (FGEW) Content |
|---|---|---|---|
| E1 | 1,000 ≤ NAMW < 10,000 | < 10 wt% below 500 Daltons < 25 wt% below | Low concern FGs:[e] no limit<br><br>Moderate-concern FGs: FGEW ≥ 1,000<br><br>Moderate-concern FGs + High concern FGs: FGEW$_{combined}$ ≥ 5,000<br><br>High-concern FGs: FGEW ≥ 5,000 |

[PAGE ]

| | | 1,000 Daltons | |
|---|---|---|---|
| E2 | NAM W $\geq$ 10,000 | < 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons | No FG restrictions |
| E3 | No limit | No limit | Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] |

[a] See 40 CFR § 723.250(b) Polymers. "Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units." [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[b] The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Elemental limitations, see 40 CFR § 723.250(d)(2) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers which degrade, decompose, or depolymerize, see 40 CFR § 723.250(d)(3) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory, see 40 CFR § 723.250(d)(4) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Water absorbing polymers with NAMW ≥ 10,000 Daltons, see 40 CFR § 723.250(d)(5) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 -

Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

c "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[7]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

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title>Federal Register</full-title></periodical><pages>16316-

16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

~~As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption".~~ [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]~~; however, t~~There are instances, however, where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc.*, in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather ~~are based~~ on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW ≥ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, ≤ 10 μm) represent a ~~general~~ class of chemical substances (hereinafter referred to as "HMW polymers") that may cause ~~an~~potential inhalation ~~toxicity~~hazards, including~~(*i.e.*,~~ lung overload[2]~~)~~ *via* ~~the~~a

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[2] Overload is defined in this article as when the exposure concentration is sufficiently high or the duration sufficiently long to overwhelm AM-mediated clearance.

specific mode(s) of action (*i.e.*, impairment of alveolar-macrophage [AM] mediated clearance), as identified in rat inhalation studies, to within chemical substances present in the respirable, poorly soluble particulates in the NCP Chemical Categories document for respirable, poorly soluble particulatesy. The focus on overload has been due to the fact that poor soluble particles appear to produce lung tumors in rats when AM-mediated clearance is over-whelmed and chronic inflammation is present. However, the chemical substances that are provided as analogues within the boundaries for the within the boundaries for the NCP Chemical Category on respirable, poorly soluble particulates are limited to discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for those polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as representative a first step with toxicological analogues withidentifying points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. An additional aim was to introduceIn addition, a new approach methodologies methodology (NAMs) was introduced as athe tiered-testing strategy to that meets the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

[PAGE  ]

## MATERIALS AND METHODS

### Systematic Literature Review

An initial literature search was conducted in November 2016, and a supplemental literature search was conducted in April 2018. The details of these reviews, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO) criteria used for reviewing results for relevance are provided in the Supporting Information file at "Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies that evaluated potential "lung overload" toxicity, *i.e.*, respiratory tract toxicity of HMW polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and alveolar regions) effects in laboratory animals and identified points of departure, or informed the mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this evaluation, "lung overload" refers to the "type of retained lung burden seen with excessively high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated particle clearance" [ ADDIN EN.CITE

<EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><DisplayText>[8]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595773878">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload

and human health risk assessment: a critical review</title><secondary-title>Inhal

Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-

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57</pages><volume>12</volume><number>1-

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Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug

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Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-

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num>10.1080/089583700196536</electronic-resource-num><remote-database-

provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>]. Since "overload" is ~~defined~~

~~manifest~~ differently in experimental animals versus humans [ ADDIN EN.CITE     ADDIN

EN.CITE.DATA    ], the literature searches used search strings that were intended to be overly

inclusive to identify studies that evaluated "overload" in both experimental animals and humans.

A secondary objective was to ~~identify~~ develop ~~potential NAMs that may be incorporated into~~ a

tiered-testing strategy that minimizes the use of vertebrate animals and can serve as a NAM for

this chemical category.

**Risk Assessment Approaches Under TSCA**

EPA generally uses ~~the~~ a margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments ~~performed~~ on new chemical substances ~~under TSCA~~. The MOE ~~approach~~ is calculated based on a point(s) of departure (POD) divided by ~~a~~ the human exposure estimate(s). The POD is ~~typically identified~~developed from an effect level ~~from a study(ies) in experimental animals~~ (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or by performing benchmark dose modeling~~benchmark dose [BMD]~~). [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-

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playText>[16]</DisplayText><record><rec-number>44</rec-number><foreign-keys><key

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Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental

Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-

title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S.

Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-

title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></reco

rd></Cite></EndNote>]. However, for chronic effects like including lung overload, the LADD

represents the more appropriate exposure metric for quantifying potential risks [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><Dis

playText>[17]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key

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nterpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable

Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

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05/documents/05-

iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record>

</Cite></EndNote>]. A summary of the default values used for in calculating PDRs and LADDs

for new chemical substances in powder or particulate form is provided in [ REF _Ref46666189

\h \* MERGEFORMAT ].

Table [ SEQ Table \* ARABIC ]. Default values used for calculating the PDR and LADD.

| Description | Equation | Parameter | Defaults | Units |
|---|---|---|---|---|
| PDR (mg/day) | $Cm \times b \times h$ | Mass concentration of chemical in air (Cm) | 5 | mg/m$^3$ |
| | | Volumetric inhalation rate (b) $(0 < b \leq 7.9)$ | 1.25 | m$^3$/hr |
| | | Exposure duration (h) $(0 \leq h \leq 24)$ | 8 | hrs/day |
| LADD[a] (mg/kg-bw/day) | $(I \times ED \times EY) /$ $(BW \times ATc \times$ 365 days/yr) | Inhalation PDR (I) | 50 | mg/day |
| | | Days exposed per year (ED) $(0 \leq ED$ (integer) $\leq 365)$ | 250 | days/site-yr |
| | | Years of occupational exposure (EY) $(0 \leq EY)$ | 40 | years |
| | | Body weight (BW) $(0 \leq ATc)$ | 80 | kg |
| | | Averaging time over a lifetime (chronic) $(0 \leq ATc)$ | 70 | years |

For each of the MOEs calculated hereinin this article, both the PDR and LADD have been provided are provided for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE is higher than the benchmark MOE, the risks are not considered a concern under TSCAchemical substance is considered as not posing a potential risk.

### Benchmark MOE Derivation

The benchmark MOE is derived to accounts for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192,

https://www.epa.gov/sites/production/files/2014-12/documents/rfd-

final.pdf</pages><volume>EPA/630/P-

02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNot

e>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability

(*i.e.*, human-to-human variability or $UF_H$), interspecies variability (*i.e.*, animal-to-human

extrapolation uncertainty or $UF_A$), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with

extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No

Observed Adverse Effect Concentration [NOAEC] or $UF_L$). The default UF values used for

calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times$

$UF_A \times UF_L = 1000$). EPA has developed guidance ~~focused on improving~~ to improve the science

underlying the animal-to-human uncertainty factor, which provides generalized procedures for

deriving dosimetric adjustment factors (DAF), which are applied to adjust exposure levels of

observed toxicity in the animals and perform interspecies extrapolation [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><Dis

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https://www.epa.gov/sites/production/files/2014-12/documents/rfd-

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02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><

Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-

number>47</rec-number><foreign-keys><key app="EN" db-

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keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>

Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</secondary-

title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>].
As described below in the section on interspecies extrapolation and overload simulations.

Application application of DAFs to the animal airborne exposure values yields estimates of the

concentration that would result in the same concentration to in humans, that is, the Human

Equivalent Concentration (HEC). For studies reporting with only a LOAEC, EPA recommends

benchmark dose modeling be performed, if the experimental data are amenable, to identify a

benchmark dose lower limit value (BMDL), as described in the next section, and thereby reduce

the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with

their potential applicability to the available studies that evaluated lung overload from HMW polymers.

## Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software (BMDS) is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not available in a study, EPA typically applies a $UF_L$ of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the $UF_L$ may be reduced from 10 to 1. The statistical lower confidence limit on the concentration at the BMD (i.e., because the BMDL) is a dose level corresponding to specific response levels near the low end of the observable range of the data that and incorporates and conveys more

[PAGE ]

information than the NOAEC or the LOAEC [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>

>]. EPA's BMD software (BMDS, ver. 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, model fit evaluated using the $\chi 2$ goodness-of-fit p-value (p > 0.1), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

### *Interspecies Extrapolation and Dosimetry Simulations Demonstrating Overload*

It has long been recognized that the external exposure concentration of particles is not the same amount that is inhaled, subsequently deposited and retained, and responsible for potential adverse health effects. Inhaled dose is dictated by particle inhalability and deposition mechanisms that can display regional and anatomical differences in the respiratory tract of experimental animals and humans at different ages~~relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages~~. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and ~~as well interact with~~by key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the

Commented [JA2]: Needed context for why the two models were being used and to connect with the benchmark MOE section. Otherwise really hard to follow.

Commented [ST3R2]: Note, Annie added this section. I accepted it, so you could see any edits, I may make

[PAGE ]

ED_005294A_00000382-00030

integrated processes of inhalability, deposition, and clearance. -Dosimetry[3] models have been

used for decades to describe the physicochemical and biological determinants of aerodynamic

behavior and toxicological responses of inhaled particles. -Such models are applied to account

for species differences in the complex interactions among the described physicochemical,

anatomical and physiological factors to determine inhaled dose metrics relevant to the mode of

action (MOA).[ ADDIN EN.CITE

<EndNote><Cite><Author>Jarabek</Author><Year>2005</Year><RecNum>81</RecNum><

DisplayText>[19]</DisplayText><record><rec-number>81</rec-number><foreign-keys><key

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type><contributors><authors><author>Jarabek, A. M.</author><author>Asgharian,

B.</author><author>Miller, F. J.</author></authors></contributors><auth-address>National

Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC,

USA.</auth-address><titles><title>Dosimetric adjustments for interspecies extrapolation of

inhaled poorly soluble particles (PSP)</title><secondary-title>Inhal Toxicol</secondary-

title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation

Toxicology</full-title></alt-periodical><pages>317-

34</pages><volume>17</volume><number>7-

8</number><edition>2005/07/16</edition><keywords><keyword>Air

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[3] Dosimetry refers to measuring or predicting the amount (*e.g.*, mass, surface area or number) of
particles in a specific region of the respiratory tract at a particular point in time. Dose metrics,
*e.g.*, deposited or retained mass in a specific region of the respiratory tract normalized to its
surface area for portal-of-entry effects, should be constructed to correspond to the MOA of the
particle and the observed toxic effect of interest.

Pollutants/*toxicity</keyword><keyword>Animals</keyword><keyword>Humans</keyword>
<keyword>*Inhalation Exposure</keyword><keyword>*Models,
Theoretical</keyword><keyword>Particle Size</keyword><keyword>Reference
Values</keyword><keyword>Reproducibility of Results</keyword><keyword>Risk
Assessment</keyword><keyword>Toxicity
Tests</keyword></keywords><dates><year>2005</year><pub-dates><date>Jun-
Jul</date></pub-dates></dates><isbn>0895-8378 (Print)&#xD;0895-8378</isbn><accession-
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num>10.1080/08958370590929394</electronic-resource-num><remote-database-
provider>NLM</remote-database-
provider><language>eng</language></record></Cite></EndNote>]. Herein, we explore two
different available dosimetry models and conduct simulations to demonstrate factors determining
overload.


### Regional ~~Dose-Deposited Dosimetry-Dose~~ Ratio (RDDR) Model (U.S. EPA, 1994)

EPA introduced formal dosimetry modeling into its derivation procedures for risk assessment of

inhaled materials with its ~~EPA may apply DAFs to PODs identified from experimental animal~~

~~studies based on the methods described in its~~ 1994 ~~guidance~~ document entitled ~~titled~~ "*Methods*

*for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*"

[ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><Dis

playText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key

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<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

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Protection Agency, Research Triangle Park, North Carolina</secondary-

title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>].

To derive a DAF for particle exposures, EPA developed a software program for calculating the

regional deposited dose ratio (RDDR), ~~that is, as~~ the DAF for insoluble particles. The RDDR is

an empirical model of deposition, ~~that is~~ applicable to particles in the size range of 0.5-30 μm

and calculates an RDDR ~~value~~ as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute

volume ($V_E$; mL/min), depositional fraction (Fr) ~~of the particulate in the~~ of the particle in the

regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a

normalizing factor (NF), such as respiratory tract surface area of the region with the observed

toxicity for portal-of-entry effects, ~~for the region of interest~~. The RDDR ~~user~~ inputs include mass

median aerodynamic diameter (MMAD), geometric standard deviation (σ) ~~for the particle of~~

~~interest~~, and the average bodyweight of the animal ~~used in the study~~ from which default $V_E$ and

surface areas of the respiratory tract regions ~~for the animal~~ are calculated. Human ventilatory parameters and assumptions regarding exposure regimen (*e.g.*, hours/day and lifetime) are analogously used in the model to predict the human deposition fraction with default values for the NF. The RDDR ~~may be~~is applied to the ~~duration~~ duration-adjusted POD, which describes the ~~; however, risk assessments performed under TSCA apply the RDDR to the POD obtained under the~~ laboratory animal regimen, to arrive at the POD$_{HEC}$. Thereafter, the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ ADDIN EN.CITE

<EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[20]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>DOSBox</author></authors></contributors><titles><title>DOSBox &quot;Way more FPA than Counterstrike !&quot;</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>].

### *Multiple-Path Particle Dosimetry (MPPD)* Model

~~Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation~~

tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ ADDIN EN.CITE
<EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum><
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B.</author></authors></contributors><auth-address>Department of Medicine, Duke University
Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-
path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl
Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the
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50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keyw
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&amp; histology/physiology</keyword><keyword>Lung/*anatomy &amp;

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Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function

Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal

Volume/physiology</keyword><keyword>Trachea/anatomy &amp;

histology/physiology</keyword></keywords><dates><year>1995</year><pub-

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num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-

provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.*

(2016) [ ADDIN EN.CITE

<EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><Di

splayText>[22]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key

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B.</author><author>Schroeter, J.D.</author><author>Price,

O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple

Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-

title></periodical><pages>14-

26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record><

/Cite></EndNote>] is a mechanistic, multipath model that ~~was modified and~~can be used to

predict deposition, clearance, and retained lung burden over the course of a long-term exposure ,
as described by Ladics *et al.* (2020) [ ADDIN EN.CITE
<EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><Di
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type><contributors><authors><author>Ladics, G.</author><author>Price,
O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson,
S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry
Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide
Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-
title></titles><periodical><full-title>Chemical Research in Toxicology</full-
title></periodical><pages>In
preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndN
ote>]. The MPPD model is supported by Applied Research Associates, Inc. (ARA) and is
available as freeware. An EPA version of MPPD is anticipated to undergo external peer review
for application to Agency assessments late FY20. As with the RDDR ~~outputs~~model, the MPPD
~~outputs~~ model provides ~~values~~predictions that may be used to calculate a $POD_{HEC}$ for inhaled
deposited dose; however, unlike the RDDR model, the MPPD model additionally provides
~~outputs~~predictions of retained dose that may be more appropriate to characterize chronic effects.
~~used to characterize acute exposures *via* deposition and subchronic/chronic exposures *via*~~
~~retained dose.~~The MPPD model also incorporates inhalability[4], covers a wider size range of

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[4] Inhalability can be defined as the probability that a particle of a given size will actually enter one of the

particles (0.01 – 100 µm), and has other added capabilities including the ability to construct simulations of activity patterns with different ventilation parameters within a given day.

To calculate clearance and thereby retained dose, The the MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title> Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models,

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respiratory tract orifices in the case of non-human primates or humans or enter the nares in the case of rodents that are obligatory nose breathers. Inhalability varies between species and is a critical adjustment for interspecies extrapolation.

[PAGE ]

Theoretical</keyword><keyword>Neoplasms, Radiation-

Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation

Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation

Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory

System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract

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urls></urls><remote-database-provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>]. These rates are considered

representative of insoluble particles. More recently, the ICRP model and clearance rates have

been updated based on improved lung burden data [ ADDIN EN.CITE ADDIN

EN.CITE.DATA ]. Refinements may be imparted by chemical-specific dissolution data and

exploration of these new model values. Hygroscopic growth is currently not addressed in either

the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers.

In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar

clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar

clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-

week rat exposures. In humans, MPPD implements the ICRP clearance model localized for

individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model

are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates

associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human

model. Additional uncertainty in the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

*Benchmark Dose Modeling*

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach, as discussed in EPA (2012)

[ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><Dis playText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote >]. When a NOAEC is not identified in a study, EPA typically applies a $UF_L$ of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the $UF_L$ may be reduced from 10 to 1, because the BMDL is a dose level corresponding to specific

response levels near the low end of the observable range of the data and incorporates and

conveys more information than the NOAEC or the LOAEC [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><Dis

playText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B

enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460</secondary-

title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection

Agency, Washington, DC 20460</full-title></periodical><pages>99,

https://www.epa.gov/sites/production/files/2015-

01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-

12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote

>]. EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous

(e.g., lesion incidence) data. All dichotomous models in the software were considered. A

benchmark response (BMR) of 10% extra risk was selected, and model fit was evaluated using

the χ2 goodness-of-fit p-value (p > 0.1), magnitude of scaled residuals at concentrations near the

BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the

model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models

providing adequate fit, per EPA's guidance [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><Dis

playText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

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timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B

enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460</secondary-

title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection

Agency, Washington, DC 20460</full-title></periodical><pages>99,

https://www.epa.gov/sites/production/files/2015-

01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-

12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote

>].

## RESULTS AND DISCUSSION

### Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract

screening, 28 articles were selected for full text review, and 23 articles were identified using

additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review,

only 24 articles contained relevant information that satisfied the PECO criteria for lung overload

from HMW polymers. In the supplemental literature search, 1218 articles were identified on

PubMed and Embase (combined). Title and abstract screening resulted in 46 potentially relevant

articles for full text screening. Of these, 13 were identified as potentially relevant for review;

seven of the 13 articles were also identified in the initial literature search. Complete details on the

systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries, to develop the health effects summaries in the section on Hazard Identification, and to identify NAMs to include in the section on Tiered-Testing Strategies.

**Category Boundaries**

The category boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>
], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed further below.

ED_005294A_00000382-00044

It should be noted that even if a HMW polymer satisfies the category boundary criteria for the category, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

In humans, Respirable respirable particles are those chemical substances with an aerodynamic particle size of less than or equal to 10 μm. The cutoff of 10 μm, as defined by EPA in its "*Air Quality Criteria for Particulate Matter*", represents "particles collected by a sampler with an upper 50% cut point of 10 μm $D_a$ [aerodynamic diameter] and a specific, fairly sharp, penetration curve" [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[26]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndN

ote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 μm diameter that are excluded from the 10 μm $D_a$ fraction [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[26]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].


In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size cuts of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 μm $D_a$ particles as an upper limit for particles with this size entering the alveolar region [ ADDIN EN.CITE

<EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><
DisplayText>[27]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-
type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title
>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-
title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures
Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American
Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed.
Vincent, J.H.</full-title></periodical><pages>240,
https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-
particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-
5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>].
Further, consideration must also be given to the particle settling that may occur rate. For example,
iIn still air, 10 μm spherical particles with a density of 1 g/cm$^3$ can remain airborne for
approximately 8 minutes [ ADDIN EN.CITE
<EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><Di
splayText>[28]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-
type><contributors><authors><author>Baron,
P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne
Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute

for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].~However, and as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 µm particles to settle in still air) [ ADDIN EN.CITE

<EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[27, 28]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>].

Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. ~~Though~~ Although occupational monitoring data provide ~~the most direct~~ assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and ~~the reality~~ that ~~nearly all~~ solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion.

For the purposes of defining this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc.*, in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 μm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, ~~a practical cutoff of >~~materials that

contain greater than or equal to 1% respirable particles by weight (wt%) based on particle size

distribution data is the practical as the cutoff for assessing respirable particles and this percentage

would be based on particle size distribution data for the material. The practical cutoff of ≥ 1 wt%

is the same cutoff EPA applies to the nonreportable content of nanoscale materials [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><Dis

playText>[29]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key

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timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>C

hemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting

and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-

title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-

3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates>

<urls></urls></record></Cite></EndNote>]. This The same cutoff would apply to the

particle/droplet size distribution in the case offor aerosols of a solid or liquid chemical substance

and would be determined based on droplet size data for the material and/or liquid application

method (*e.g.*, spray, aerosol, mist).


EPA's Functional Group (FG) and Functional Group Equivalent Weight (FGEW) criteria for E1

polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of

HMW polymers. Therefore, we propose using these criteria as an initial screen for determining

whether a HMW polymer is considered non-reactive and included or reactive and included or

> **Commented [ST4]:** There were previous edits from EPA, but
> not Annie. This seems awkward to me. I think the original text was
> clearer. Thoughts?
>
> Another option is: "respirable particles that are greater than or
> equal to 1% by weight (wt%) based on particle size distribution data
> for the material is the practical inclusion cutoff for assessing
> respirable particles and is the same cutoff EPA applies to the
> nonreportable content of nanoscale materials"

excluded from the category, respectively. As shown in [ REF _Ref46665925 \h \*

MERGEFORMAT ], the E1 polymer exemption criteria include low-concern, moderate-concern,

or high-concern FGs. A summary of rRepresentative FGs meeting each of these hazard concern

levels is shown in [ REF _Ref46674358 \h \* MERGEFORMAT ].



**Figure [ SEQ Figure \* ARABIC ].** FG hazard concern levels for polymeric substances meeting

EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for

identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern)

for the HMW polymer category. The following cutoffs are proposed as the category boundaries

for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-

concern FGs (FGEW $\geq$ 1,000), or high-concern FGs (FGEW $\geq$ 5,000). "R" represents an

undefined structure; "X" represents a halide. See: EPA (1997) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><Dis

playText>[7]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>P

olymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-

03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-

001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]

for further details.


A ~~generally recognized~~ property of respirable, low reactive (*i.e.*, low toxicity) particles that ~~can~~

may cause lung overload is the poorly soluble nature of these compounds. EPA has published

general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L),

slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (>

1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><Dis

playText>[30]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>S

ection 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM,

Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution

Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW,

Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution

Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW,

Washington, DC 20460</full-title></periodical><pages>22,

https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-

748-B12-

001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

These values were not established for evaluating the solubility of particles for lung overload;

however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [

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<EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><D

isplayText>[31]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key

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type><contributors><authors><author>OECD</author></authors></contributors><titles><title

>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline

for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for

Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-

ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-

chemical-

properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls

></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW

polymers. ECETOC (2013) [ ADDIN EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><

DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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type><contributors><authors><author>ECETOC</author></authors></contributors><titles><tit

le>Poorly Soluble Particles / Lung Overload</title></titles><pages>130,

http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No.

122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre

for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical

Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-

content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-

Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial

biosolubility screening approach that provided qualitative determinants (*i.e.*, "soluble",

"insoluble", "Low dissolution rate", or "Very high dissolution rate") for assessing biosolubility;

however, no quantitative thresholds were provided. In comparison, the International Commission

on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and

Health (FIOSH) provided quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day$^{-1}$), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day$^{-1}$), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day$^{-1}$) [

ADDIN EN.CITE

<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title> Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract
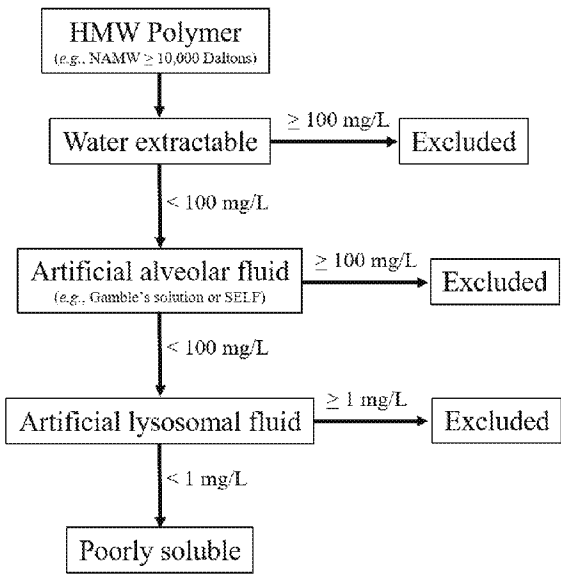
Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)&#xD;0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of $\leq$ 1 mg/L in artificial lung fluids for identifying particles as "low soluble dusts" [ ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[33]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed ~~previously~~above, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are $\leq$ 10 μm and $\geq$ 1 wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW

polymer. However, determining whether a HMW polymer is "poorly soluble" and a potential hazard concern for lung overload is also dependent on the potential daily exposure estimates. Therefore, we propose using the inclusion/exclusion cutoffs shown in [ REF _Ref46673847 \h \* MERGEFORMAT ], which consider water extractability/ or biosolubility and the legally binding permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and Health Administration (OSHA) for respirable particulates not otherwise regulated or (PNOR) (*i.e.*, 5 mg/m$^3$).

**Scheme [ SEQ Scheme \* ARABIC ].** Screening criteria for determining water extractability and biosolubility.
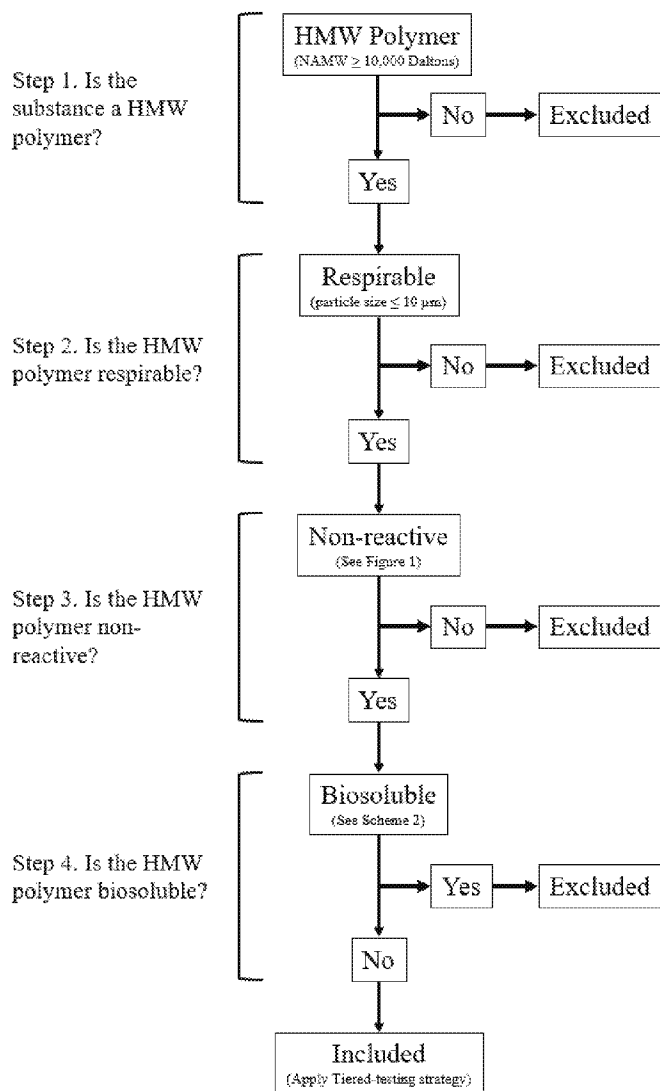
The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first ~~screen~~ step is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been ~~established to correlate~~ correlated with either biosolubility or biopersistence. Therefore, EPA's cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected ~~rather than the low water solubility cutoff~~, since it ~~represents a transition from slight to moderate water solubility and~~ is ~~therefore~~ expected to be conservatively inclusive ~~in the first step because water extractability is generally expected~~and to overestimate the insolubility of polymers in biological fluids. In the second ~~screen~~step, ~~two~~ biosolubility cutoffs ~~may be used,~~are either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the OSHA PNOR PEL of 5 mg/m$^3$ (*i.e.*, 50 mg/day; 5 mg/m$^3$ × 10 m$^3$/day) for the respirable fraction, defined based on size selective characteristics as particles smaller than 10 μm aerodynamic diameter. The ~~first value is based on EPA (2020) where the Agency applied a~~ biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid ~~. This value would~~ equates to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ ADDIN EN.CITE

<EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum>< DisplayText>[34]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German FIOSH biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

**Scheme [ SEQ Scheme \* ARABIC ].** Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.

[PAGE  ]

**Step 1. Is the substance a HMW polymer?**

HMW Polymer
(NAMW ≥ 10,000 Daltons)

No → Excluded

Yes

**Step 2. Is the HMW polymer respirable?**

Respirable
(particle size ≤ 10 μm)

No → Excluded

Yes

**Step 3. Is the HMW polymer non-reactive?**

Non-reactive
(See Figure 1)

No → Excluded

Yes

**Step 4. Is the HMW polymer biosoluble?**

Biosoluble
(See Scheme 2)

Yes → Excluded

No

Included
(Apply Tiered-testing strategy)

Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons)

[PAGE ]

materials, which meet the ~~above-stated~~ criteria for these parameters. HMW polymers ~~meeting these criteria are those which~~ are typically formed through various polymerization processes~~.~~ ~~Chemical substances,~~ included ~~are~~ branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [ REF _Ref46674591 \h  \* MERGEFORMAT ].

[ EMBED ChemDraw.Document.6.0 ]

**Figure [ SEQ Figure \* ARABIC ].** Representative members of the HMW polymer category. Structure A, on the left, is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers ($NR'_2$ replaces OR' or OR'') may also be present. Structure B, on the right, is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C, on the bottom, is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

## Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The

systematic review of the literature was used to identify inhalation studies that assessed endpoints

indicative of "overload" for potential toxicological analogues. For the purpose of defining this

chemical category, overload has the same definition as identified by EPA (1996) [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><Dis

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A

ir Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of

Research and Development, U.S. Environmental Protection Agency, Washington, DC

20460</secondary-title></titles><periodical><full-title>Office of Research and Development,

U.S. Environmental Protection Agency, Washington, DC 20460</full-

title></periodical><pages>774,

http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/

600/P-

95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndN

ote>]: "This is defined as the overwhelming of macrophage-mediated clearance by the deposition

of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific

effect noted in experimental studies, generally in rats, using many different kinds of poorly

soluble particles (including $TiO_2$, volcanic ash, diesel exhaust particles, carbon black, and fly

ash) and results in A [alveolar] region clearance slowing or stasis, with an associated

inflammation and aggregation of macrophages in the lungs and increased translocation of

particles into the interstitium." The relevant studies ~~that were identified~~ are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload ~~of some~~for new chemical substances.

*Human Data*

The hazard concerns discussed ~~herein~~ are limited to chronic effects in the ~~lower respiratory tract~~pulmonary (alveolar) region of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies ~~have shown that~~with rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ ADDIN EN.CITE

<EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[38]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-

title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that "evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group". It has also been reported that "epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases" [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of "all-cause" or "cause-specific" mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. Aside from this one epidemiological study on toner exposures, the ~~available studies that evaluated evaluation potential hazards from~~of exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 "Experimental Animal Inhalation Studies on HMW Polymers" of the Supplemental Information file.

*Animal Data - Noncancer Effects*

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good

laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m$^3$ (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm$^3$) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m$^3$. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-

360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><

urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-

resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m$^3$.


Bellmann *et al.* (1992) [ ADDIN EN.CITE

<EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><

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H.</author><author>Creutzenberg, O.</author><author>Mermelstein,

R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und

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Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-

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91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Anim

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rd><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

effects/enzymology</keyword><keyword>Macrophages/*drug

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Factors</keyword></keywords><dates><year>1992</year><pub-

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num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed

an additional 13-week study using the same test substance ~~used by~~as Muhle *et al*. (1990) [

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<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><Di

splayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key

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W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow,

P.</author><author>Kilpper, R.</author><author>Mackenzie,

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R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in

Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m$^3$ (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm$^3$) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m$^3$ and not reversible at 40 mg/m$^3$ [ ADDIN EN.CITE

<EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)&#xD;0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>].

Muhle *et al.* (1991) [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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[ ADDIN EN.CITE
<EndNote><Cite><Author>Bellmann</Author><Year>1991</Year><RecNum>3</RecNum><

DisplayText>[44]</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844572">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Kilpper, R.</author><author>MacKenzie, J. C.</author><author>Morrow, P.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats</title><secondary-title>Fundam Appl Toxicol</secondary-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>300-13</pages><volume>17</volume><number>2</number><edition>1991/08/01</edition><keywords><keyword>Aerosols</keyword><keyword>Animals</keyword><keyword>Body Burden</keyword><keyword>Dust/adverse effects</keyword><keyword>Female</keyword><keyword>Half-Life</keyword><keyword>Lung/*metabolism</keyword><keyword>Lymph Nodes/metabolism</keyword><keyword>Male</keyword><keyword>Pulmonary Alveoli/metabolism</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Sex Factors</keyword><keyword>Silicon Dioxide/*metabolism</keyword><keyword>Titanium/*metabolism</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590 (Print)&#xD;0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m$^3$ (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm$^3$) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies and under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m$^3$, with a NOAEC of 1 mg/m$^3$.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al.* (1990, 1991) and Bellman *et al.* (1991, 1992) [ ADDIN EN.CITE ADDIN EN.CITE.DATA   ] showed similar effects similar to those in rats [ ADDIN EN.CITE ADDIN EN.CITE.DATA   ]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m$^3$ for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m$^3$ for the remaining timetest period. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters

(increased cell number, macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m$^3$.

Muhle *et al.* (1990) [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m$^3$ (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm$^3$) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled ($^{85}$Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week)

to PVC powder at concentrations $\geq 3.3$ mg/m³. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m³. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m³, respectively, supporting that lung overload occurred at concentrations $\geq 3.3$ mg/m³ for this water-insoluble polymer.

*Animal Data - Cancer*

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580&#xD;Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url>&lt;Go to ISI&gt;://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>]. No increased in the incidence of tumors incidence was observed in either study; however, interstitial and alveolar lung pathology has been documented in long-term inhalation studies on these polymers. See section on "Animal Data - Noncancer Effects" above.

*Supporting Information*

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ ADDIN EN.CITE      ADDIN EN.CITE.DATA     ] developed an *in vitro* assay to test nanoparticles for predicting biologically active toxicity from passive (*i.e.*, overload condition) toxicity. The assay uses used rat NR8383 alveolar macrophages in cell culture

medium incubated with test material ~~in cell culture medium, and~~to assesses toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours)~~in the cell culture supernatant~~. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. The size and shape of the test substances ranged from 9 nm to <30 μm and from 15 $m^2$/g to 200 $m^2$/g. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/$m^3$ for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay used a particle surface area-based threshold of <6000 $mm^2$/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL) to determine the biological relevance of the lowest observed significant *in vitro* effects ~~threshold for active toxicity was a surface-area/volume concentration of 6,000 $mm^2$/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in μg/mL)~~ in at least two of the four measured parameters ~~measured in supernatant~~. The results for the nanomaterials ~~tested~~ showed good ~~correspondence~~ correlation between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

**Quantitative Points of Departure (PODs)**

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ ADDIN EN.CITE     ADDIN EN.CITE.DATA    ]. This study did not report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [ REF _Ref46678612 \h \* MERGEFORMAT ]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure regimenfrequency, and aerodynamic particle size (MMAD and, GSD, and density).

Each study was evaluated to determine whether the data were amenable for BMD modeling.

For the polyacrylates and methacrylates subcategory, sSeveral subchronic studies , for the polyacrylates and methacrylates subcategory that met the initial POD selection criteria, are included in [ REF _Ref46678612 \h \* MERGEFORMAT ] that met the initial POD selection criteria; however, BMD modeling was not performed on these studies because chronic studies

were available and ~~deemed~~ considered more relevant for ~~the~~ hazard assessment with identifying health protective PODs. Two chronic studies met the POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. BMD modeling was performed ~~for the data in~~on the rat study performed by Muhle *et al.* (1991) [ ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580&#xD;Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel

exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords
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0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-

urls><url>&lt;Go to ISI&gt;://WOS:A1991FZ99700006</url></related-urls></urls><electronic-

resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-

num><language>English</language></record></Cite></EndNote>] , asbecause it used a longer

exposure duration, was published in a peer-reviewed journal, and did not change exposure

concentrations during the study. , whereas, in tThe hamster study, modified the exposure

concentrations were modified after the first five months. Among tThe endpoints affected at the

LOAEC in that the rat study (macrophages, PMN, and lymphocytes in BAL; incidence of

pulmonary fibrosis), only the incidence of fibrosis incidence could be modeled, as the BALF

parameters were reported without measures of variability (*i.e.*, standard deviation or standard

error). The incidences of lung fibrosis (summed across severity categories) were subjected to

BMD modeling, as described in Section 3 "Benchmark Dose (BMD) Modeling Outputs" of the

Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m$^3$, as shown

in [ REF _Ref46678612 \h \* MERGEFORMAT ].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the

alveolar clearance for the tracer was not possible because of the absence of reported measures of

variability ([ REF _Ref46678612 \h \* MERGEFORMAT ]).

**Table [ SEQ Table \\* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m$^3$) | NOAEC (mg/m$^3$) | LOAEC (mg/m$^3$) | BMCL (mg/m$^3$) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| *Polyacrylates and Methacrylates Sub-category* | | | | | | | |
| 9000 Toner (styrene/butylmethacrylate random copolymer) | SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery | 0, 1, 4, or 16 | 1 | 4 | 2.5 (fibrosis) | Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis | [ ADDIN EN.CITE ADDIN EN.CITE.DATA   ] |

[PAGE  ]

**Table [ SEQ Table \* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| 9000 Toner (styrene/butylmet | Syrian Golden Han:AURA Hamster, male and female, | 0, 1.5, 6, or 24 (months 1-5); 0, | ND | 1.5-4 | Not derived; variable | Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation of particle-laden macrophages in lungs; interstitial | [ ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[51]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho [PAGE ] Institute</a |

**Table [ SEQ Table \* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| Toner A (styrene/butylmet hacrylate random | F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6 | 0, 4, 16, or 64 | ND | 4 | Not derived | Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs | [ ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[45]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunho [PAGE ] fe Institute</a |

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| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | | | [ ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author> |

**Table [ SEQ Table \\* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | | | [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be |

**Table [ SEQ Table \* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| Toner B (styrene/ butadiene random copolymer) | F344 rat, female (50 rats/group for main study) up to 6 mo. | 0, 1, 4, 16, or 64 | 4 | 16 | Not derived | Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs | [ ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[52]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer [PAGE ] Institute</a |

**Table [ SEQ Table \\* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
| *Polyvinyls Sub-Category* | | | | | | | |

**Table [ SEQ Table \* ARABIC ].** Available PODs for inhalation studies on HMW Polymers.

| Test material | Strain, Species, Sex, Exposure frequency and duration, Recovery | Exposure Concentrations (mg/m³) | NOAEC (mg/m³) | LOAEC (mg/m³) | BMCL (mg/m³) | Lung Effects at LOAEC | Reference |
|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  | [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,</author><author>Be |

*Study Selection for establishing sub-category points of departure (PODs)*

In rats, the key events in the development of lung tumors ~~in rats~~ in response to inhalation of

inorganic PSPs of low toxicity (as outlined by ECETOC 2013 [ ADDIN EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><

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le>Poorly Soluble Particles / Lung Overload</title></titles><pages>130,

http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No.

122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre

for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical

Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-

content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-

Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al.*, 2018 [

ADDIN EN.CITE     ADDIN EN.CITE.DATA     ], Driscoll and Borm, 2020 [ ADDIN EN.CITE

<EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><

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type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.&#xD;Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.&#xD;Nanoconsult BV, Meerssen, The Netherlands.&#xD;Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data as reviewed herein suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages, thereby leading to tumor formation in humans. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [ REF _Ref46678612 \h  \* MERGEFORMAT ], PODs of 2.5 mg/m$^3$ and 3.3 mg/m$^3$ were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a $BMCL_{10}$ of 2.5 mg/m$^3$ for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study on this sub-category of materials and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-

title></periodical><pages>374-

377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-

3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for

identifying a LOAEC of 3.3 mg/m$^3$ for the polyvinyls sub-category because it was based on

decreased alveolar clearance, which is the first key event in the proposed adverse outcome

pathway for lung overload from PSPs in the rat [ ADDIN EN.CITE     ADDIN EN.CITE.DATA

 ]. These study PODs represent potential starting points for evaluating new chemical substances

that fit within one of the HMW polymer sub-categories. EPA may determine that either of these

PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-

categories but are anticipated to have ~~comparable or greater~~a potential for ~~causing~~ lung overload

in the rat than the new chemical substance under evaluation. For example, EPA generally uses

the POD of 3.3 mg/m$^3$ for quantifying the potential risks of HMW polymers, even for

chemistries that would not fall within the polyvinyls sub-category, based on the properties of the

new chemical substance ~~compared to the PVC powder~~. Notwithstanding this, we recognize that

data on a new chemical substance or an alternative analogue would take precedence over using

one of these analogues as the default POD, if EPA concludes there are no study limitations on

the new chemical substance or alternative analogue that would preclude the use of those data.


Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used

to make inferences about HMW polymers. Compared to systemic effects, lung overload

responses to inorganic PSPs show large variations in susceptibility between and among

mammalian species, with the rat being the only species to develop lung tumors [ ADDIN

EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><

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http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No.

122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

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content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-

Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific

response has been explained by species differences in the accumulation of insoluble and

respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs

(*e.g.*, crystalline silica). For example, hHumans are at least six times more resistant to attaining

lung overload conditions than rats for the following reasons: human alveolar macrophages

(AMs) are larger (*i.e.*, average volume = 4,990 $\mu m^3$) than rat AMs (*i.e.*, average volume = 1,166

$\mu m^3$); humans have a greater number of AMs (*i.e.*, average = $7.0 \times 10^9$) than rats (*i.e.*, average =

$2.6 \times 10^7$); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 $\mu m^2$/AM) than

rat AMs (*i.e.*, average = 140,000 μm$^2$/AM) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ].

Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula

*et al*. (2001) [ ADDIN EN.CITE

<EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><D

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type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan,

V.</author><author>Green, F. H.</author><author>Hahn, F.

F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute,

Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure

concentration or dose on the distribution of particulate material in rat and human

lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-

title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ

Health Perspect</full-title></periodical><pages>311-

8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keyw

ords><keyword>Adult</keyword><keyword>Air

Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</key

word><keyword>Dose-Response Relationship,

Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhala

tion Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages,

Alveolar</keyword><keyword>Male</keyword><keyword>Middle

Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational

Exposure</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Vehicle Emissions/*analysis</keyword></keywords><dates><year>2001</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0091-6765 (Print)&#xD;0091-6765</isbn><accession-num>11335177</accession-num><urls></urls><custom2>PMC1240269</custom2><electronic-resource-num>10.1289/ehp.01109311</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] showed that "the relative amounts of intraluminal and interstitial particle load differ markedly between rats and humans with particles being found predominantly in the interstitium in man and intra-luminarly in rats." In rats, accumulation of particulate matter in the intraluminal space leads to adverse "alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses" [ ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

As noted previously, EPA generally uses the polyvinyls sub-category analogue (*i.e.*, PVC powder) POD of 3.3 mg/m$^3$ for evaluating new chemical substances that may present a lung overload hazard when the chemical properties are comparable ~~between the new chemical substance and the PVC powder~~. The polyvinyls sub-category POD is then subject to the established EPA dosimetry adjustment. Each of these approaches is discussed below. These dosimetric adjustments may also be applied to the polyacrylates/methacrylates sub-category analogue (9000 Toner), as well as to data on new chemical substances or other potential analogues that fit within the chemical boundaries for this category.

As shown in [ REF _Ref519678474 \h \* MERGEFORMAT ], the RDDRs for the PVC powder ranged from 0.501 in the pulmonary region (PU) ~~up~~ to 2.248 in the tracheobronchial (TB) region. Since the effects occurred in the PU region, the PU (surface area: 0.34 m$^2$ [rat]; 54 m$^2$ [human]) RDDR was used for deriving a POD$_{HEC}$, as follows:

$$POD_{HEC} = POD \times RDDR_{PU}$$

or

$$POD_{HEC} = 3.3 \text{ mg/m}^3 \times 0.5 = 1.65 \text{ mg/m}^3$$

Table [ SEQ Table \* ARABIC ]. Depositional fractions and RDDRs for rats and humans.[a]

| SPECIES | Extrathoracic (ET) | | Tracheobronchial (TB) | | Pulmonary (PU) | | Thoracic (TB + PU) | | Total Respiratory Tract (RT) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Surface Area (cm$^2$) | Depositional Fraction | Surface Area (cm$^2$) | Depositional Fraction | Surface Area (m$^2$) | Depositional Fraction | Surface Area (m$^2$) | Depositional Fraction | Surface Area (m$^2$) | Depositional Fraction |
| Rat | 15 | 0.33 | 22.5 | 0.068 | 0.34 | 0.061 | 0.342 | 0.129 | 0.344 | 0.459 |
| Human | 200 | 0.24 | 3200 | 0.059 | 54 | 0.267 | 54.32 | 0.125 | 54.34 | 0.566 |
| RDD | 0.075 | 1.373 | 0.007 | 1.15 | 0.006 | 0.229 | 0.006 | 1.028 | 0.006 | 0.811 |
| RDDR | 0.252 | | 2.248 | | 0.501 | | 0.863 | | 1.763 | |

[a] Inputted values included: MMAD = 1.30; GSD = 2.07; density = 1.3 g/cm$^3$.

[PAGE ]

In comparison, the MPPD model was used to conduct simulations to predict retained mass burden in the PU region of female F344 rats exposed in the Muhle *et al.* (1990) [ ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. The geometry model in the MPPD software for the Sprague-Dawley rat was used, but with the Agency default body weight (BW) of 229 grams for female F-344 rats in a chronic study [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-

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Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

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11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>]. The MPPD software internally scales ventilation parameters and respiratory volumes based

on BW, so this resulted in tidal volume ($V_T$) of 1.54, a breathing frequency of 166 bpm,

functional residual capacity (FRC) of 3.01 mL, and an upper respiratory tract (URT) volume of

0.34 mL. The 229 g rat PU surface area is predicted to be 1997 $cm^2$. The particle MMAD, GSD

of the particle size distribution, and its density were: 1.3 $\mu$m, 2.07, and 1.3 $g/cm^3$, respectively.

The regimen and duration of the nose-only exposure in the Muhle *et al.* (1990) [ ADDIN

EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><Di

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M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust

overloading of lungs after exposure of rats to particles of low solubility: Comparative

studies</title><secondary-title>Journal of Aerosol Science</secondary-

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title></periodical><pages>374-

377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-

3</electronic-resource-num></record></Cite></EndNote>] study was 5 h/d and 5 d/w for 8

months and was used in the simulation. We note that there were discrepancies in the reported

duration of exposure of 7 months versus 8 months in Muhle *et al.* (1990) [ ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><Di

splayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key

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overloading of lungs after exposure of rats to particles of low solubility: Comparative

studies</title><secondary-title>Journal of Aerosol Science</secondary-

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title></periodical><pages>374-

377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-

3</electronic-resource-num></record></Cite></EndNote>]. However, the Bellmann *et al.*

(1986) [ ADDIN EN.CITE

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type><contributors><authors><author>Bellmann, B.</author><author>Muhle,

H.</author><author>Creutzenberg, O.</author></authors></contributors><titles><title>The

Effect of a &quot;Nuisance&quot; Dust Inhalation of Lung Clearance</title><secondary-

title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol

Conference</secondary-title></titles><periodical><full-title>Aerosols, Formation and

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title></periodical><pages>209-

211</pages><dates><year>1986</year></dates><urls></urls></record></Cite></EndNote>]

abstract consistently reported an 8-month exposure duration; therefore, a duration of 8-months

was used.

Using the above experimental conditions, the predicted retained mass in the PU region of F344

rats, shown in [ REF _Ref46766078 \h \* MERGEFORMAT ], demonstrated the goodness of fit

of the MPPD model to the experimental data reported by Muhle *et al.* (1990) [ ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><Di

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M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust
overloading of lungs after exposure of rats to particles of low solubility: Comparative
studies</title><secondary-title>Journal of Aerosol Science</secondary-
title></titles><periodical><full-title>Journal of Aerosol Science</full-
title></periodical><pages>374-
377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>
<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-
3</electronic-resource-num></record></Cite></EndNote>]. For example, Muhle *et al.* (1990) [
ADDIN EN.CITE
<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><Di
splayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key
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type><contributors><authors><author>Muhle, H.</author><author>Bellmann,
B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar,
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377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] reported a retained PU mass of 0.56 mg in rats exposed to 3.3 mg/m$^3$; the MPPD model predicted a retained PU mass of 0.63 mg at this exposure concentration. Additional simulations were conducted using the same three exposure concentration as Muhle *et al.* (1990) [ ADDIN EN.CITE

<EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>], but the key input parameters for MMAD, GSD, and density were varied and bounded. Details on the additional simulations are provided under "Section 4 MPPD Modeling Outputs" of the Supporting Information file. These additional simulations reinforce that prediction of overload kinetics is specific to the particle physicochemical properties (size, distribution, and density) and experimental regimen. Such

simulation demonstrations can be useful to defining whether a given particle and exposure conditions achieve overload.
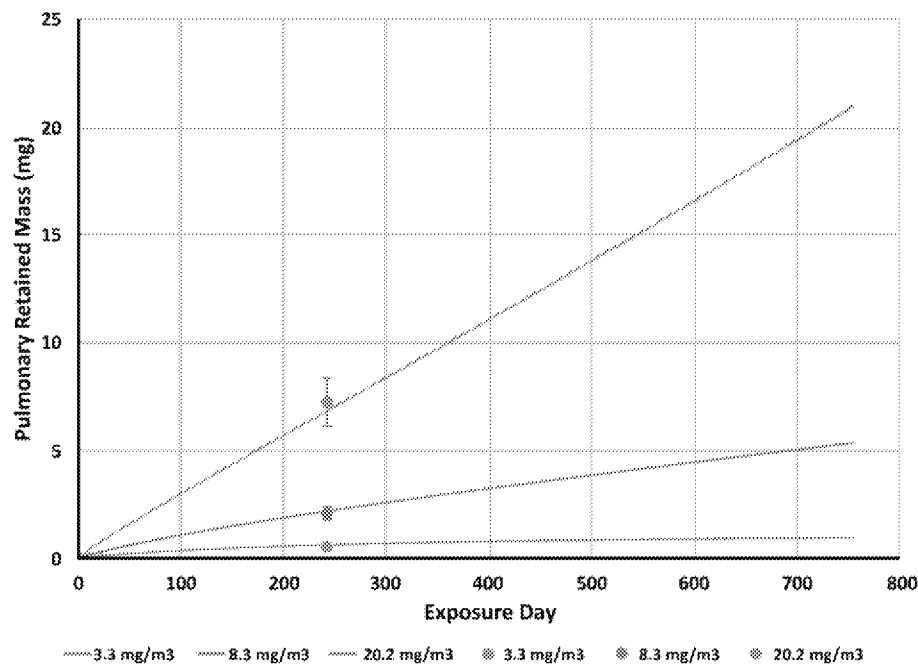


**Figure [ SEQ Figure \\* ARABIC ].** MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar,

M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 μm, a GSD of 2.07, and a density of 1.3 $g/cm^3$ for three concentrations (3.3, 8.3, and 20.2 $mg/m^3$). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

For extrapolation of the predicted rat retained PU mass to an HEC, human simulations were conducted for adult males with a $V_T$ of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) [ ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann

ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)&#xD;0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and represent ventilation associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of $V_T$ and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value ($V_E$) found in [ REF _Ref46666189 \h \* MERGEFORMAT ] of 1.25 $m^3$/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in $cm^2$ according to the established US EPA methods [ ADDIN EN.CITE

&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;EPA&lt;/Author&gt;&lt;Year&gt;1994&lt;/Year&gt;&lt;RecNum&gt;47&lt;/RecNum&gt;&lt;DisplayText&gt;[18]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;47&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909"&gt;47&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;EPA&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry&lt;/title&gt;&lt;secondary-title&gt;Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina&lt;/secondary-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina&lt;/full-title&gt;&lt;/periodical&gt;&lt;pages&gt;389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf&lt;/pages&gt;&lt;volume&gt;EP/600/9-90/066F&lt;/volume&gt;&lt;dates&gt;&lt;year&gt;1994&lt;/year&gt;&lt;/dates&gt;&lt;urls&gt;&lt;/urls&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. The MPPD model estimates a human pulmonary surface area of 66.3 $m^2$ for an 80 kg adult male. As shown in [ REF _Ref46767442 \h \* MERGEFORMAT ], simulations were performed iteratively to arrive at an HEC that achieved the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions reported by Muhle *et al.* (1990) [ ADDIN EN.CITE

&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Muhle&lt;/Author&gt;&lt;Year&gt;1990&lt;/Year&gt;&lt;RecNum&gt;13&lt;/RecNum&gt;&lt;DisplayText&gt;[48]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;13&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key

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overloading of lungs after exposure of rats to particles of low solubility: Comparative

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377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-

3</electronic-resource-num></record></Cite></EndNote>]. As was shown in [ REF

_Ref46766078 \h \* MERGEFORMAT ], the predicted retained mass in the PU region

corresponds well with the observed experimental data. The last two rows of [ REF

_Ref46767442 \h \* MERGEFORMAT ] demonstrate the difference in HEC value due to

variation in ventilatory parameters associated with either light or heavy activity.

Table [ SEQ Table \* ARABIC ]. MPPD predictions and HEC calculations for Muhle *et al.* (1990) study of F344 rats exposed to PVC with a particle MMAD of 1.3 μm, GSD of 2.07 and density of 1.3 gm / cm$^3$.

| Exposure Concentration (mg/m$^3$) | 3.3 | 8.3 | 20.2 |
|---|---|---|---|
| Experimental Rat Retained PU Mass (mg) | 0.56±0.16 | 2.09±0.29 | 7.24±1.10 |
| Predicted Rat Retained PU Mass (mg) | 0.63 | 2.21 | 6.88 |
| Predicted Rat Retained PU Mass / PU SA (mg/m$^2$) | 2.8 | 10.5 | 36.3 |
| Light Activity 40-Year HEC (mg/m$^3$) | 0.33 | 1.23 | 4.25 |

[PAGE ]

| Heavy Activity 40-Year HEC (mg/m$^3$) | 0.14 | 0.53 | 1.84 |
|---|---|---|---|

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

*Category benchmark margin of exposure (MOE)*

EPA currently applies a ~~benchmark MOE composite UF~~ of 1,000 ~~as the benchmark MOE for~~to the PVC powder POD of 3.3 mg/m$^3$. The composite UF consists of default values of 10 for UF$_H$, UF$_A$, and UF$_L$. This default approach was initially established as a conservative means of evaluating new chemistries on HMW polymers, which were anticipated to present a hazard concern for lung overload. ~~However, s~~Several refinements to these values may be made, ~~including reducing.~~ the ~~The~~ TK and TD components of the UF$_A$ value and reducing the UF$_L$. Dosimetric adjustments using the RDDR model or the MPPD model, as discussed above, may be applied to calculate a POD$_{HEC}$, thereby reducing the TK component of the UF$_A$ to 1. Since lung overload is a chronic effect that is manifested primarily based on the retained dose in the PU region, the RDDR model is not necessarily the most appropriate for deriving a POD$_{HEC}$, given that deposition is a more relevant metric for short-term effects/exposures. However, the RDDR model was used to provide comparative estimates of the MOE to the ~~other approaches versus the~~ respective benchmark MOE, given that the RDDR ~~approach~~ model is recommended in EPA guidance as the default for quantifying POD$_{HEC}$s for particles. For the TD component, a reduced value of 1 may be applied based on the proposal from the ILSI Workshop Consensus Report on rat lung response to particle overload, which stated: "For both neoplastic and fibrogenic endpoints in the rat, associated with PSP exposures, the work group proposed that the TD component of the interspecies UF be reduced from a factor of 3 to 1, given that chronic active

[PAGE ]

inflammation in the rat appears to be a more sensitive response than in other species, including humans" [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. The $UF_L$ may be reduced from 10 to 1 for the PVC powder analogue POD because default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathwaythis dose represented the point at which retardation of alveolar clearance started, based on the retained mass of about 0.5 mg/lung. This approach is consistent with EPA (2002) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>], which states that the $UF_L$ "may be altered, depending on the magnitude and nature of the response at the LOAEL". Further, the default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway. Based on the foregoing considerations, the following values are proposed for deriving the benchmark MOE for HMW

polymers, which are generally applicable regardless of whether the POD is derived from an analogue or a new chemical substance.

$UF_H = 10$: The default value of 10 should be applied, unless there are human data showing which age groups or time periods are the most sensitive to lung overload. This approach is consistent with EPA's guidance for reducing the default $UF_H$ [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

$UF_A = 3$ or 1: A reduced value of 1 should be applied for the TD component based on the ~~proposal~~ consideration documented by Olin (2000). In addition, if the data are amenable for deriving a $POD_{HEC}$, the dosimetric adjustment for the TK component further supports reducing

this UF [ ADDIN EN.CITE

&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;EPA&lt;/Author&gt;&lt;Year&gt;2002&lt;/Year&gt;&lt;RecNum&gt;46&lt;/RecNum&gt;&lt;Dis

playText&gt;[14, 18]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;46&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595788591"&gt;46&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-

type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;EPA&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;A

Review of the Reference Dose and Reference Concentration Processes&lt;/title&gt;&lt;secondary-

title&gt;Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC

20460&lt;/secondary-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460&lt;/full-title&gt;&lt;/periodical&gt;&lt;pages&gt;192,

https://www.epa.gov/sites/production/files/2014-12/documents/rfd-

final.pdf&lt;/pages&gt;&lt;volume&gt;EPA/630/P-

02/002F&lt;/volume&gt;&lt;dates&gt;&lt;year&gt;2002&lt;/year&gt;&lt;/dates&gt;&lt;urls&gt;&lt;/urls&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;Cite&gt;&lt;

Author&gt;EPA&lt;/Author&gt;&lt;Year&gt;1994&lt;/Year&gt;&lt;RecNum&gt;47&lt;/RecNum&gt;&lt;record&gt;&lt;rec-

number&gt;47&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-

id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909"&gt;47&lt;/key&gt;&lt;/foreign-

keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-

type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;EPA&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;

Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

Dosimetry&lt;/title&gt;&lt;secondary-title&gt;Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina&lt;/secondary-

title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina&lt;/full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

$UF_L$ = 10 or 1: A value of 1 should be applied when the POD is based on a study NOAEC or when BMD modeling is applied to derive a BMCL, per EPA guidance [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The default value of 10 should be applied when the POD is based on a study LOAEC; however, a reduced value may be used, when ~~for example,~~ the LOAEC is based on key event 1 from the proposed adverse outcome pathway for PSPs. Reductions in the $UF_L$ based on other key

[PAGE  ]

events should be made on a case-by-case basis and supported by discussion of the key event within the context of an established AOP.

The default and dosimetrically adjusted PODs and benchmark MOEs derived on new chemical substance risk assessments are used to inform risk management options for addressing potential risks. Therefore, values derived using dosimetric adjustments may allow for refined estimates For example, the default POD of 3.3 mg/m³ and benchmark MOE of 1,000 result in an MOE of 2.0E-01 that would require for determining the appropriate engineering controls and/or a respirator with an applied protection factor (APF) of 1,000 personal protective equipment. In comparison, when dosimetric adjustments are applied using the MPPD modeling outputs, the POD$_{HEC\ light\ activity}$ of 0.33 mg/m³ and refined benchmark MOE of 10 result in an MOE 1.7, which indicates that engineering controls and/or a respirator with an APF of 10 would be required.

*Uncertainties and Limitations*

The available toxicological studies for HMW polymers lack data on materials with molecular weights < 70,000 Daltons [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>63</RecNum><DisplayText>[59]</DisplayText><record><rec-number>63</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803909">63</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>High Molecular Weight Polymers in the New Chemicals Program</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</full-

title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-

substances-control-act-tsca/high-molecular-weight-polymers-

new</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

In addition, the following uncertainties and study limitations were noted, that if known, may

serve to refine the boundaries for this category:

- Physicochemical properties can influence deposition of inhaled particles (*e.g.*, particle
  size, distribution, density, and hygroscopicity) while and biopersistence and bioreactivity
  (*e.g.,* solubility, surface chemistry, and composition). determine biopersistence and
  bioreactivity and thereby impact clearance and retention. However, the available studies
  of test materials in this category are generally missing information on these properties,
  with the exception of particle size.

- Information on molecular weight was not reported for test materials used in the studies of
  the PVC powder [ ADDIN EN.CITE
  <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecN
  um><DisplayText>[48]</DisplayText><record><rec-number>13</rec-
  number><foreign-keys><key app="EN" db-
  id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
  timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal
  Article">17</ref-type><contributors><authors><author>Muhle,

H.</author><author>Bellmann, B.</author><author>Creutzenberg,

O.</author><author>Heinrich, U.</author><author>Ketkar,

M.</author><author>Mermelstein,

R.</author></authors></contributors><titles><title>Dust overloading of lungs after

exposure of rats to particles of low solubility: Comparative studies</title><secondary-

title>Journal of Aerosol Science</secondary-title></titles><periodical><full-

title>Journal of Aerosol Science</full-title></periodical><pages>374-

377</pages><volume>21</volume><number>3</number><dates><year>1990</year></

dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-

8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>].

- The test materials administered in the 9000 toner studies [ ADDIN EN.CITE     ADDIN

  EN.CITE.DATA     ] included colorant materials (predominantly carbon black) at up to

  10%, and the influence of these colorants on the observed effects is unknown.

- The PODs summarized in [ REF _Ref46678612 \h  \* MERGEFORMAT ] for the HMW

  polymers were reported on a mass/volume basis. However, there is evidence that number

  of particles, particle volume, and/or volume of particles retained in the lung can influence

  the threshold at which lung overload conditions occur [ ADDIN EN.CITE     ADDIN

  EN.CITE.DATA     ]. Thus, particle density may be an important consideration in

  identifying a POD; however, the appropriate density metric and how density should be

  incorporated remain uncertain. Data emerging on nanomaterials and ambient ultrafine

  particles also increasingly suggest surface area may determine toxicity. Thus, different

  internal dose metrics should be explored. This can be done readily with dosimetry models

  as described.

- Particle morphology, reactive groups, and cytotoxicity can impede clearance pathways and induce other mechanisms of toxicity in rodents and humans. These factors include covalent binding to lung tissues, toxicity to clearance macrophages/cilia and particles lodging in pulmonary tissues which may not be considered in aerodynamic models. An *in vitro* macrophage clearance assay utilizing human or primate cells and rat cells would be potentially useful information to determine whether new chemistries fall within or outside the boundaries for this category.

An additional, important consideration pertains to the uncertainty ~~associated~~ association ~~with~~ of the human relevance of lung tumors observed in rats exposed to PSPs. ~~The available data clearly demonstrate that the rat is a sensitive model for non-neoplastic pulmonary effects following repeated exposure to PSPs, which have also been shown to occur in occupational cohorts (e.g., coal miners).~~ The rat ~~also~~ appears to be unique among species with regard to carcinogenesis in the lung due to particle overload. Lung tumors following chronic exposure to PSPs have been reported in rats, but have not been reported in mice, hamster, non-human primates, or humans [

ADDIN EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No.

122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre

for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical

Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-

content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-

Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. Despite the uncertainty

in the carcinogenicity of inhaled PSPs, the rat model remains a useful model for lung overload

because it is a sensitive model for inflammatory response to PSPs, and ~~because~~ protecting

against inflammation and proliferation may also protect against tumor formation [ ADDIN

EN.CITE    ADDIN EN.CITE.DATA    ].


**Tiered-testing Strategy**


The POD and benchmark MOE derived herein provide an analogue/read-across approach for

assessing new chemical substances that fit within the chemical category boundaries for HMW

polymers~~, also defined herein~~. As with any analogue read-across, assessors must carefully

consider the comparability of the new chemical substance to the analogue or another acceptable

toxicological analogue~~.; this~~ This framework provides specific criteria for evaluating whether a

new chemical substance "fits" into the HMW polymer category (*i.e.*, not chemically reactive,

insoluble in water, not expected to be directly cytotoxic, not expected to release toxic

degradates). Additionally, we demonstrate the utility of dosimetry modeling to inform evaluation

or experimental design.

When If information is not available to evaluate whether the new chemical substance fits within the category boundaries and the analogue is appropriate forno acceptable toxicological analogue is available for use in a risk assessment, testing should be performed to aid with refining the evaluation of new chemistries that are anticipated tomay present a potential lung overload hazard. A tiered-testing strategy that is consistent with the reduced vertebrate testing requirements under the amended TSCA is provided. Though this strategy does not completely exclude vertebrate testing, it maximizes the use of NAMs for determining whether vertebrate testing should be considered. This strategy incorporates *in chemico* and/or *in vitro* characterization of the chemical substance in Tier I (*e.g.*, particle physical characteristics, size distribution, density, reactivity, and biosolubility measurements). For substances that have particles in the respirable range, are non-reactive, and are not biosoluble, computational screening is included under Tier II to determine whether the HMW polymer is estimated to exceed the clearance t½ in the rat or demonstrate overload under anticipated use conditions. If the HMW polymer is expected to exceed the clearance t½ in the rat, then risk management options or strategic *in vivo* testing is proposed as a final option under Tier III.

**Commented [ST5]:** Comment from Ann: "Can we add a statement that if the PMN submitter prefers not to use the EPA "analog", they may generate the data on their specific HMW polymer?"

TS: Does the correction to the text make this clear? Can't believe I overlooked that typo so many times.

**Commented [ST6]:** Comment from Stephanie: "There is no density characterization in Tier I. Do we want to mention it here?"

TS: If this is not a routine measure for HMW polymers, we should add it to the testing since it will be needed to do the model simulations.

**Tier I**

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- **Particle Size Distribution** or Aerosolized Droplet Size of particle in use (*i.e.*, cascade impactor, laser methods, *e.g.*, OECD TG 110 [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>64</RecNum><DisplayText>[61]</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-

**Formatted:** Font: Bold

id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595804668">64</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>OECD</author></authors></contributors><titles

><title>Particle Size Distribution/Fibre Length and Diameter

Distributions</title><secondary-title>OECD Guideline for Testing of

Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for

Testing of Chemicals</full-title></periodical><pages>13, https://www.oecd-

ilibrary.org/environment/test-no-110-particle-size-distribution-fibre-length-and-diameter-

distributions_9789264069688-

en</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></r

ecord></Cite></EndNote>], OPPTS 830.7520 [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>65</RecNu

m><DisplayText>[62]</DisplayText><record><rec-number>65</rec-number><foreign-

keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595804850">65</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles>

<title>Particle Size, Fiber Length, and Diameter Distribution</title><secondary-

title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency,

1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-

title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S.

Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</full-title></periodical><pages>13, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]) of the new chemical substance during specific use(s) (*i.e.*, depending on the intended or known uses of the chemical substances, particle size distribution may need to be tested under more than one use scenario)

- o If the % of respirable particles (*i.e.*, ≤ 10 μm) is less than 1 wt% under the conditions of use, or following transport, stop at Tier I.

- o If the % of respirable particles (*i.e.*, ≤ 10 μm) is greater than 1 wt% under the conditions of use, or if respirable particles are anticipated or shown to be generated following transport (> 1%), then proceed with reactivity testing, if needed, or biosolubility testing.

- **Reactivity**

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  - o If the HMW polymer is a potential concern for reactivity, based on ~~function or~~ other information (*e.g.*, does not meet the E1 FG/FGEW criteria), reactivity should be assessed using an *in vitro* method, preferably discussed with EPA in a pre-notice consultation meeting and prior to study initiation. The assay developed by Wiemann *et al.* (2013) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ] provides a potential option; however, there are caveats with its use, such as not being validated and uncertainty with whether the test method could be used with HMW polymers, underscoring the recommendation to consult with EPA prior to testing using this method or other test methods.

[PAGE ]

- If substance is "reactive" (*e.g.*, does not met the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, it would be excluded from the HMW polymer category. If evidence indicates the substance is "non-reactive" (*e.g.*, it does meet the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, then proceed to biosolubility testing.

- **Biosolubility Testing**
  - Solubility in Gamble's solution (*e.g.*, ECETOC, 2013 [ ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum> 9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of

[PAGE ]

Chemicals</publisher><work-type>Technical Report</work-

type><urls><related-urls><url>http://www.ecetoc.org/wp-

content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-

Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]),

simulated epithelial lung fluid (SELF) (*e.g.*, Boisa *et al.* 2014 [ ADDIN EN.CITE

ADDIN EN.CITE.DATA ]); and/or phagolysosomal simulant fluid (*e.g.*,

BAUA, 2017 [ ADDIN EN.CITE

<EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57

</RecNum><DisplayText>[33]</DisplayText><record><rec-number>57</rec-

number><foreign-keys><key app="EN" db-

id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>BAUA</author></authors></contributors

><titles><title>Methodology for the Identification of Granular Biopersistent

Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for

Occupational Safety and Health</secondary-title></titles><periodical><full-

title>Federal Institute for Occupational Safety and Health</full-

title></periodical><pages>103,

https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates>

<year>2017</year></dates><urls></urls></record></Cite></EndNote>])

o Employ a simple exponential decay model to predict the dissolution half-life: P(t)=P0e$^{-rt}$, where: P(t) = the amount of some quantity at time t; P0 = initial amount at time t = 0; r = the decay rate; t = time

The exponential decay function is the solution to the first order reaction equation, assuming a constant decay rate, r:

$$\frac{dP(t)}{dt} = -rP(t), P(0) = P_0$$

First order kinetics are used as the basis for lung clearance rates including dissolution and absorption into blood [ ADDIN EN.CITE     ADDIN EN.CITE.DATA    ].

▪ If the solubility data indicate a dissolution rate (*i.e.*, 100 mg/L/day or 72 mg/day) higher than the daily occupational exposure estimate (*e.g.*, default PDR of 50 mg/day), then stop at Tier I.
▪ If the solubility data indicate a dissolution rate lower than the daily occupational exposure estimate, then proceed with Tier II testing.

If the % of respirable particles is > 1 wt%, the HMW polymer is non-reactive, and the HMW polymer has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

**Tier II**

• Perform computational modeling (*e.g.*, MPPD) ~~including the effect of dissolution~~ to predict deposition, clearance, and lung burden for a simulated chronic rat exposure (See, *e.g.*, Ladics *et al.*, 2020 [ ADDIN EN.CITE

[PAGE  ]

<EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[23]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]). If dissolution data are not available, assume the test substance is poorly soluble.

- If the clearance t½ is less than 60 daysMPPD simulations do not indicate overload under the conditions of use, stop at Tier II.

If the clearance t½ is greater than that for PSPs in the rat (*i.e.*, 60 days) simulations indicate overload under the conditions of use, consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

**Tier III**

- Strategic *in vivo* testing should be considered, albeit on a case-by-case basis, and after discussions with EPA at a pre-notice consultation meeting. When performed, the testing should include:

  o MPPD simulations to predict deposited and retained mass for the specific particle size, distribution, and density of the new chemical substance to identify exposure levels where overload is likely to occur.

  o Exposure at concentrations that allow for a concentration-response for low exposures, where pulmonary clearance is not impaired, and a high enough toexposure that demonstrates impaired pulmonary clearance of particles and lead to an "overload" condition. It has been shown that in rats impaired clearance starts when phagocytized particle volume exceeds 6% of normal alveolar macrophage volume and clearance stops altogether when phagocytized volume reaches 60% of normal macrophage volume (See, *e.g.*, Borm *et al.*, 2015 [ ADDIN EN.CITE ADDIN EN.CITE.DATA ]); and

  o Special attention to pulmonary function tests; blood oxygen ($pO_2$); lung burden measurements and lung clearance kinetics; collection of BALF for assessment of marker enzyme activities, total protein content, and cell counts; lung retention and clearance; lung weight; and lung histopathology (inflammation and cell proliferation). It is not necessary to evaluate internal organs. OECD TG 413 [

ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>71</RecNum><DisplayText>[66]</DisplayText><record><rec-number>71</rec-

[PAGE ]

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><titles><title>90-Day (Subchronic) Inhalation Toxicity

Study</title><secondary-title>OECD Guideline for Testing of

Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for

Testing of Chemicals</full-title></periodical><pages>23, https://www.oecd-

ilibrary.org/environment/test-no-413-subchronic-inhalation-toxicity-90-day-

study_9789264070806-

en</pages><volume>413</volume><dates><year>2018</year></dates><urls></

urls></record></Cite></EndNote>] and OECD GD 39 [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>72

</RecNum><DisplayText>[67]</DisplayText><record><rec-number>72</rec-

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><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on

Testing and Assessment (Second Edition)</title><secondary-title>Environment

Directorate Joint Meeting of the Chemicals Committee and the Working Party on

[PAGE  ]

Chemicals, Pesticides and Biotechnology</secondary-

title></titles><periodical><full-title>Environment Directorate Joint Meeting of

the Chemicals Committee and the Working Party on Chemicals, Pesticides and

Biotechnology</full-title></periodical><pages>106,

https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm

/mono(2009)28/rev1&amp;doclanguage=en</pages><volume>ENV/JM/MONO(

2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></rec

ord></Cite></EndNote>] should be consulted, given that the 90-day subchronic

inhalation toxicity study in rats (OECD 413) with a 60-day recovery period is

sufficient for identifying lung overload for PSPs in this species [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</

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<titles><title>TSCA New Chemicals Program (NCP) Chemical

Categories</title><secondary-title>Office of Pollution Prevention and Toxics,

U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW,

Washington, DC 20460</secondary-title></titles><periodical><full-title>Office

of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200

[PAGE ]

Pennsylvania Ave., NW, Washington, DC 20460</full-

title></periodical><pages>https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><da

tes><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

The utility of studies of ~~Research is ongoing to evaluate if studies utilizing~~ shorter

exposure duration (*e.g.*, 5 days) followed by recovery ~~is still being investigated,~~

~~may be useful,~~ therefore, if submitters ~~are interested in evaluating the utility of a~~

~~shorter duration study, such studies~~ should ~~be discussed~~ discuss the applicability

of such studies with EPA prior to ~~study~~ initiation.


**CONCLUSIONS**

In summary, the available toxicological studies on HMW polymers support that the key

parameters for determining whether a HMW polymer may present a hazard based on lung

overload include: respirability, reactivity, and solubility. These are the same key parameters for

lung overload caused by poorly soluble particles (PSP), an extensively studied and ~~well~~

~~known~~well-known phenomena. ~~-~~The tiered strategy~~approaches~~ proposed in this ~~paper~~article

takes advantage of these key factors and evaluates ~~identified for lung overload and apply, as~~their

applicab~~le~~ility to HMW polymers. ~~-~~Two HMW polymers were ~~-~~identified as toxicological

analogues ~~were identified~~ that may be used for "read across" when evaluating the potential of a

~~to~~ new chemical substance ~~for evaluating~~to result in lung overload. When applicable, the PODs

on these analogues may be refined using dosimetry modeling such as simulations with the MPPD

model to predict ~~when~~the exposure levels when overload might occur in the experimental

species~~The MPPD software provides for a straightforward approach to predict when overload~~

~~might occur in the experimental species,~~ to perform interspecies extrapolation to HEC estimates, and to inform inferences for human health risk ~~evaluation~~assessment. For new chemical substances that are not suitable for read across from these toxicological analogues, or when a company prefers to provide data for its specific HMW polymer new chemical substance, the tiered-testing strategy described above provides a framework that minimizes the use of vertebrate animals, and takes advantage of new alternative ~~method~~assays to characterize ~~and~~ key events in a putative AOP for ~~from~~ PSP induced lung overload; ~~with~~while providing information which may be used to determine if there is a potential for ~~informing whether~~for new HMW polymers to present a hazard for lung overload under its condition(s) of use. ~~Concentrations at which overload was not achieved in the rat are relevant to human assessment, as are other endpoints other than tumors at overload.~~ Collectively, the read across approach, ~~Simulations~~ the MPPD model simulations, and the tiered-testing strategy represent a novel approach method that will aid with evaluating new chemical substances to ensure that they do not present an unreasonable risk to human health and advancing the understanding of inhaled particle toxicity~~would also be most useful to design of experiments before costly investments in inhalation studies are made.~~ Using these approaches, data on the respirability, reactivity and solubility of HMW polymers will be evaluated by EPA and only when needed, on a case by case basis, will animal studies be considered and discussed with the new chemical substance manufacture. ~~and may also help to~~resulting in a reduction and ~~refiment~~refinement of ~~reduce and refine~~ the number of animals used. The tiered testing approach was developed based on the best available science currently available. It is expected that as new data ~~will be~~is provided to EPA through new substance notifications, ~~and will be evaluated as appropriate to determine if~~ the tiered testing framework

~~requires modification~~will be evaluated and updated as appropriate. ~~-~~This is in line with EPA's Strategic Plan to Promote the Development and Implementation of Alternative Test Methods.

## ASSOCIATED CONTENT

**Supporting Information**.

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. Experimental Animal Inhalation Studies on HMW Polymers

Section 3. Benchmark Dose (BMD) Modeling Outputs

Section 4: MPPD Modeling Outputs

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**Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ~~‡These authors contributed equally. (match statement to author names with a symbol)~~

EPA sponsored the initial literature review through a government contract to SRC (68HERH19F0197 (TO#07))[insert number]. The American Chemistry Council's TSCA Section 5 Testing Consortium sponsored an updated literature review by an independent third party.ACC sponsored the supplemental literature review conducted by an independent third party.

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**Notes**

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

**ACKNOWLEDGMENT**

Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).

**REFERENCES**

[ ADDIN EN.REFLIST ]

**From:** Hayes, Mike [hayes.mp@pg.com]
**Sent:** 7/31/2020 1:14:24 PM
**To:** Stedeford, Todd [Stedeford.Todd@epa.gov]; Stefan Moors [stefan.moors@basf.com]; Keene, Athena [Athena.Keene@AftonChemical.com]; Kennedy, Wayne [Wayne.Kennedy@AftonChemical.com]; Rick_Becker@americanchemistry.com; Sahar_Osman-Sypher@americanchemistry.com; Hillebold, Donna [donna.hillebold@nouryon.com]; ljovanovich@stepan.com; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Skulsky, Joseph [JSkulsky@stepan.com]; Washburn, Kenneth [Kenneth.Washburn@us.sasol.com]; Yang, Xinyu [xyang@Solenis.com]; Ann Tveit [ann.tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Salazar, Keith [Salazar.Keith@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]
**CC:** Tremblay, Raphael [tremblay.r.2@pg.com]
**Subject:** RE: Revised draft surfactants manuscript - please see attached
**Attachments:** draft manscript general surfactants - 29 July 2020.ver.3 RT.docx

Todd,

# Ex. 5 Deliberative Process (DP)

Best regards,
Raphael and Mike

**From:** Stedeford, Todd <Stedeford.Todd@epa.gov>
**Sent:** Friday, July 31, 2020 8:30 AM
**To:** Stefan Moors <stefan.moors@basf.com>; Hayes, Mike <hayes.mp@pg.com>; Keene, Athena <Athena.Keene@AftonChemical.com>; Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Rick_Becker@americanchemistry.com; Sahar_Osman-Sypher@americanchemistry.com; Hillebold, Donna <donna.hillebold@nouryon.com>; ljovanovich@stepan.com; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Ann Tveit <ann.tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
**Subject:** RE: Revised draft surfactants manuscript - please see attached

Agreed!

**From:** Stefan Moors <stefan.moors@basf.com>
**Sent:** Friday, July 31, 2020 8:28 AM
**To:** Hayes, Mike <hayes.mp@pg.com>; Keene, Athena <Athena.Keene@AftonChemical.com>; Kennedy, Wayne

<Wayne.Kennedy@AftonChemical.com>; Rick_Becker@americanchemistry.com; Stedeford, Todd
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<donna.hillebold@nouryon.com>; ljovanovich@stepan.com; Ogden, Julianne
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<Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Ann Tveit <ann.tveit@basf.com>; Irwin,
William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek,
Annie <Jarabek.Annie@epa.gov>
**Subject:** RE: Revised draft surfactants manuscript - please see attached

Dear Todd / all

# Ex. 5 Deliberative Process (DP)

Mit freundlichen Grüssen / Best regards
**Stefan Moors**
Manager Product Safety, Eurotox and DGPT registered toxicologist

Phone: +49 211 7940-5888, Email: stefan.moors@basf.com
Postal Address: BASF Personal Care and Nutrition GmbH, GBP/RD, Gebäude Z22, Henkelstrasse 67, 40589
Duesseldorf, Germany

**◻◼BASF**

We create chemistry

**From:** Hayes, Mike <hayes.mp@pg.com>
**Sent:** Thursday, July 30, 2020 9:33 PM
**To:** Keene, Athena <Athena.Keene@AftonChemical.com>; Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Becker, Rick <Rick_Becker@americanchemistry.com>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Osman-Sypher, Sahar <Sahar_Osman-Sypher@americanchemistry.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; Jovanovich, Lela <ljovanovich@stepan.com>; Stefan Moors <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Ann Tveit <ann.tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
**Subject:** RE: Revised draft surfactants manuscript - please see attached

Todd,

# Ex. 5 Deliberative Process (DP)

Best regards,
Mike

**From:** Keene, Athena <Athena.Keene@AftonChemical.com>
**Sent:** Thursday, July 30, 2020 11:38 AM

**To:** Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Becker, Rick <Rick_Becker@americanchemistry.com>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Osman-Sypher, Sahar <Sahar_Osman-Sypher@americanchemistry.com>; Hayes, Mike <hayes.mp@pg.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; Jovanovich, Lela <ljovanovich@stepan.com>; Moors, Stefan <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Tveit, Ann <Ann.Tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
**Subject:** RE: Revised draft surfactants manuscript - please see attached

Hi Todd,

# Ex. 5 Deliberative Process (DP)

Kind regards,
Athena

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**From:** Kennedy, Wayne
**Sent:** Thursday, July 30, 2020 10:49 AM
**To:** Becker, Rick <Rick_Becker@americanchemistry.com>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Osman-Sypher, Sahar <Sahar_Osman-Sypher@americanchemistry.com>; Hayes, Michael <hayes.mp@pg.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; Jovanovich, Lela <ljovanovich@stepan.com>; Keene, Athena <Athena.Keene@AftonChemical.com>; Moors, Stefan <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Tveit, Ann <Ann.Tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
**Subject:** RE: Revised draft surfactants manuscript - please see attached

Hello Todd,

No show stoppers that I noticed.  I included my comments in the attached document. **Ex. 5 Deliberative Process (DP)**

# Ex. 5 Deliberative Process (DP)

Regards,
Wayne


**Wayne Kennedy** | **Afton Chemical Corporation** | **Senior Manager – Product Stewardship and Regulatory Affairs** ehs

**From:** Becker, Rick <Rick_Becker@americanchemistry.com>
**Sent:** Thursday, July 30, 2020 10:23 AM
**To:** Stedeford, Todd <Stedeford.Todd@epa.gov>; Osman-Sypher, Sahar <Sahar_Osman-Sypher@americanchemistry.com>; Hayes, Michael <hayes.mp@pg.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; Jovanovich, Lela <ljovanovich@stepan.com>; Keene, Athena <Athena.Keene@AftonChemical.com>; Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Moors, Stefan <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Tveit, Ann <Ann.Tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
**Subject:** Revised draft surfactants manuscript - please see attached

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This email originated from outside of your organization. Do not click links or open attachments unless you recognize the source of this email and know the content is safe. If unsure report it to IT ServiceDesk.

Hi Todd - please see attached. I didn't see anything that was a true show stopper.

# Ex. 5 Deliberative Process (DP)

But since time is tight, if not able to include these with the submission, we can address these when doing the revision in response to peer reviewers comments.

# Ex. 5 Deliberative Process (DP)

Thanks

Rick

*Richard A. Becker Ph.D. DABT* | American Chemistry Council
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**Sent:** Wednesday, July 29, 2020 4:18 PM
**To:** Osman-Sypher, Sahar; Becker, Rick; Hayes, Michael; Hillebold, Donna; Jovanovich, Lela; Keene, Athena M.; Kennedy, Wayne; Moors, Stefan; Ogden, Julianne; Skulsky, Joseph; Washburn, Kenneth; Yang, Xinyu; Tveit, Ann; Irwin, William; Salazar, Keith; Henry, Tala; Jarabek, Annie
**Subject:** Revised draft surfactants manuscript
**Importance:** High

All,

Please find the attached, revised draft of the surfactants manuscript. This still needs a good critical review by multiple sets of eyes. This is a standalone document. It contains all of the tables. I linked up everything with the exception of the POD table. I still need to link the references in that table with EndNote. Otherwise, please review as quickly as you can.

Thank you,


Todd

# Surfactants Category: The Application of New Approach Methodologies (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

*Tala R. Henry[a,‡], Keith Salazar[b,‡], Michael P. Hayes[c], Wayne Kennedy[d], Athena M. Keene[d], Annie Jarabek[e], Stefan Moors[f], Lela Jovanovich[g], Raphael Tremblay[c], Ann Tveit[f], Richard A. Becker[h], Sahar Osman-Sypher[h], Patrick D. McMullen[i], Scott D. Slattery[i], William Irwin[b], Marc Odin[j], Julie Melia[j], and Todd Stedeford[a,]\**

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**KEYWORDS** (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval.

**ABSTRACT**

The Toxic Substances Control Act (TSCA) requires anyone who plans to manufacture (including import) a new chemical substance for a non-exempt commercial purpose to provide EPA with a premanufacture notice (PMN) before initiating the activity. Surfactants are a class of chemicals commonly used in occupational settings, in consumer products and in biological research and development and therefore subject to PMN. Their use in such applications provide pathways of exposure by which potential toxicity of these compounds may occur to humans. While TSCA requires submission of any existing toxicity data, it does not require generation of toxicity data for the purpose of or prior to PMN submission. TSCA requires EPA to review the PMN to determine whether the new chemical substance presents an unreasonable risk of injury to human health or

[PAGE ]

the environment and also mandates that EPA reduce and replace vertebrate animals in testing, to the extent practicable and scientifically justified. EPA therefore relies on a number of approaches that do not rely on *de novo* toxicity testing. Analogue read-across, in which toxicity data for a chemical of similar structure and activity is used to assess the new chemical, and chemical categories (a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity) have been used by EPA for decades to assess new chemical substances. This investigation was conducted to identify surfactant chemicals with toxicity data relevant for use in conducting quantitative human health risk assessment for new surfactant substances and define a TSCA New Chemical Category for surfactants. Category boundaries are defined, toxicological analogues suitable for conducting 'read-across' hazard assessment (*i.e.*, hazard identification and dose-response analysis) are identified and a tiered-testing strategy aimed at using new approach methodologies (NAMs) to reduce or replace animal testing is outlined. This surfactant category provides a pragmatic and scientifically defensible approach to facilitate EPA's review of new surfactant PMNs and a strategic testing approach that provides the data needed to conduct or refine surfactant risk assessment while also meeting the requirements of TSCA to reduce vertebrate testing.

## INTRODUCTION

The Toxic Substances Control Act (TSCA) was amended in 2016 by the Frank R. Lautenberg Chemical Safety for the 21$^{st}$ Century Act (Pub. L. 114-182. The amended TSCA included substantial changes to EPA's authorities and responsibilities, including requirements on EPA to make a determination regarding sufficiency of information, production quantities relative to environmental releases and human exposure and unreasonable risks. The amended TSCA also included provisions

mandating EPA "reduce and replace, to the extent practicable, scientifically justified" the use of vertebrate animals in the testing of chemicals substances. Specifically, TSCA section 4(h) charges EPA with encouraging and facilitating –

(1) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under TSCA;

(2) the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category; and

(3) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests, provided that such consortia make all information from such testing available to the Administrator.

The present investigation advances each of these TSCA mandates for chemical substances characterized as surfactants.

A surfactant is a substance that reduces the surface tension of a liquid in which it is dissolved. They are surface-active, amphiphilic compounds that self-assemble to form micelles or aggregates above a critical concentration, referred to as the critical micelle concentration (CMC). These substances are commonly used in occupational settings, in consumer products (*e.g.*, household cleaning products, personal care products, *etc.*), and in biological research and development (R&D) as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. Their use in such applications provide pathways of exposure by which potential toxicity of these

compounds may occur to human or environmental receptors. Specifically, the inherent properties of surfactants may induce toxicity if exposures occur such that they can interfere with biological surfactants or tissues. For example, sodium dodecyl sulfate, a strong anionic surfactant, is used in R&D applications at concentrations up to 10% to disrupt cell membranes and to denature proteins, whereas octylphenoxypolyethoxyethanol, a mild nonionic surfactant, is used in R&D applications at concentrations up to 1% to disrupt cell membranes, while preserving proteins for isolation [ ADDIN EN.CITE

<EndNote><Cite><Author>Burden</Author><Year>2012</Year><RecNum>14727</RecNum><DisplayText>[1]</DisplayText><record><rec-number>14727</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017177">14727</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Burden, D.W.</author></authors></contributors><titles><title>Guide to the Disruption of Biological Samples - 2012, Version 1.1.</title><secondary-title>Random Primers</secondary-title></titles><periodical><full-title>Random Primers</full-title></periodical><pages>1-25</pages><number>12</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Hazard concerns for surfactants were historically focused on their observed environmental effects and potential toxicity to aquatic organisms [ ADDIN EN.CITE     ADDIN EN.CITE.DATA    ]. For example, the U.S. Environmental Protection Agency (EPA) established chemical categories for cationic (quaternary ammonium) and anionic surfactants based on environmental toxicity concerns [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>14729</RecNum><DisplayText>[3]</DisplayText><record><rec-number>14729</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017536">14729</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>157, https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Surfactants may also be a potential hazard concern to humans, depending on the use and route of exposure, because they can disrupt the normal architecture of the lipid bilayer and reduce the surface tension, thereby solubilizing cell membranes. Mucous membranes are particularly sensitive to the surface-active effects of surfactants, which have been shown to cause irritancy and injury to the eye, based on their ability to "readily penetrate the sandwiched aqueous and lipid barriers of the cornea" [
ADDIN EN.CITE
<EndNote><Cite><Author>Fox</Author><Year>2008</Year><RecNum>14730</RecNum><DisplayText>[4]</DisplayText><record><rec-number>14730</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017801">14730</key></foreign-keys><ref-type name="Book

Section">5</ref-type><contributors><authors><author>Fox, D.A.</author><author>Boyes, W.K.</author></authors><secondary-authors><author>Klaassen, C.D.</author></secondary-authors></contributors><titles><title>Toxic Responses of the Ocular and Visual System</title><secondary-title>Casarett &amp; Doull&apos;s Toxicology - The Basic Science of Poisons, Seventh Edition</secondary-title></titles><pages>665-697</pages><section>17</section><dates><year>2008</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill, Medical Publishing Division</publisher><urls></urls></record></Cite></EndNote>].

Depending on the conditions of use, inhalation exposures to workers and/or consumers may be possible that warrant consideration in quantitative risk assessments. As noted, surfactants may cause adverse effects on mucous membranes, including the respiratory tract, and have been shown to interfere with the natural pulmonary surfactants, resulting in reduced oxygen content of arterial blood (*i.e.*, impaired gas exchange in the lung), increases in pulmonary extravascular water volume and wet-to-dry weight ratio of the lungs, grossly visible pulmonary edema, and atelectasis [ ADDIN EN.CITE     ADDIN EN.CITE.DATA    ]. However, the chemical space for surfactants that may present inhalation hazards has not been previously defined, and the potential for inhalation toxicity ranges by orders of magnitude, such as octylphenoxypolyethoxyethanol, a nonionic surfactant 14-day lowest-observed-adverse-effect concentration [LOAEC] of 5.3 mg/m$^3$) [ ADDIN EN.CITE     ADDIN EN.CITE.DATA    ], versus didecyldimethyl ammonium chloride, a cationic surfactant and biocide (DDAC, CASRN 7173-51-5; 4-week lowest-observed-adverse-effect concentration [LOAEC] of 0.08 mg/m$^3$ for portal-of-entry effects) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><

DisplayText>[10]</DisplayText><record><rec-number>14732</rec-number><foreign-

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Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>S

ubchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of

Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington,

D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and

Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-

title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-

0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]

.


The objectives of the present investigation were to: (1) perform a systematic review of the literature with the aim of defining the chemical space for surfactants; (2) identify appropriate toxicological analogues, when available, for identifying potential inhalation hazards and when data allow, identifying quantitative point(s) of departure for use in an inhalation risk assessment; (3) describe scientifically sound new approach methodologies (NAMs) to reduce or replace animal testing, where possible; and (4) establish a tiered-testing strategy, that utilizes NAMs, as appropriate, for new chemistries in the surfactant space.


**MATERIALS AND METHODS**

**Systematic Literature Review**

Two literature searches were performed, an initial search in November 2016 and a supplemental search in April 2018. The details of these searches, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcome (PECO) criteria used for reviewing the relevance of the results are provided in the Supporting Information file at "Section 1 Systematic Literature Review". These searchers were conducted with the primary objective of identifying studies that evaluated the toxicity of surfactants in respiratory tract in exposed humans, laboratory animals, and at the cellular level in *in vitro* and *ex vivo* studies. A secondary objective of these searches was to identify potential NAMs that could inform a tiered-testing strategy for general surfactants that reduces or replaces the use of vertebrate animals in regulatory testing.

**Risk Assessment Approaches under TSCA**

*Risk Assessment Paradigm*

The current methods and approaches for assessing risks of new chemical substances under TSCA have been built upon decades of expert development, scientific peer review, refinement, and scientific knowledge. Generally, EPA conducts risk assessments following the four-step process articulated by the National Research Council, first in 1983 [ ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>1983</Year><RecNum>14733</RecNum><DisplayText>[11]</DisplayText><record><rec-number>14733</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018654">14733</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>

Risk Assessment in the Federal Government: Managing the Process, Washington, D.C. The

National Academies Press</title></titles><pages>191, DOI:

https://doi.org/10.17226/366</pages><volume>ISBN: 978-0-309-03349-

7</volume><dates><year>1983</year></dates><urls></urls></record></Cite></EndNote>]

and reaffirmed several times since [ ADDIN EN.CITE

<EndNote><Cite><Author>NRC</Author><Year>1994</Year><RecNum>14734</RecNum><

DisplayText>[12, 13]</DisplayText><record><rec-number>14734</rec-number><foreign-

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Article">17</ref-

type><contributors><authors><author>NRC</author></authors></contributors><titles><title>S

cience and Judgment in Risk Assessment, Washington, D.C. The National Academies

Press</title></titles><pages>672, DOI: https://doi.org/10.17226/2125</pages><volume>ISBN:

978-0-309-07490-

2</volume><dates><year>1994</year></dates><urls></urls></record></Cite><Cite><Author>

NRC</Author><Year>2009</Year><RecNum>14737</RecNum><record><rec-

number>14737</rec-number><foreign-keys><key app="EN" db-

id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019010">14737</key></foreign-

keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>NRC</author></authors></contributors><titles><title>S

cience and Decisions: Advancing Risk Assessment, Washington, D.C. The National Academies

Press</title></titles><pages>422, DOI: https://doi.org/10.17226/12209</pages><volume>ISBN:

978-0-309-12046-

3</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>].
This process includes hazard identification, dose-response analysis, exposure assessment, and risk characterization. Hazard assessment (also called effects assessment in some EPA guidance documents) identifies the types of adverse health or environmental effects or hazards that can be caused by exposure to the chemical substance. The dose-response assessment describes the relationship between the exposure or dose of a chemical and the occurrence of health or environmental effects or outcomes is assessed. The exposure assessment characterizes the extent of human or environmental exposures, including the magnitude, frequency, and duration of the exposure, to the extent necessary and practicable within the context of the assessment. Finally, the risk characterization integrates the hazard, dose-response, and exposure components to describe the nature, and when possible, the magnitude of risks to human health and the environment.

The approaches employed for these components, including, for example, the level of detail and complexity of quantitative aspects may vary across different risk assessments and typically align with specific legislative and regulatory frameworks. For example, legislative and regulatory frameworks for hazard evaluation of pesticide active ingredients, anti-microbial substances, inerts, *etc*. are described in regulations for pesticides, which include multiple and specific requirements for toxicity data. Under TSCA and its implementing regulations [ ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>14738</RecNum><DisplayText>[14]</DisplayText><record><rec-number>14738</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596019129">14738</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA </author></authors></contributors><titles><title>40 CFR Part 720 - Premanufacture Notification</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/part-720</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], companies are required to submit a Premanufacture Notice (PMN) along with all available data on: chemical identity, production volume, byproducts, use, environmental release, disposal practices, and human exposure. These submissions are required to include all existing health and environmental data in the possession or control of the submitter, parent company, or affiliates, and a description of any existing data known to or reasonably ascertainable by the submitter. However, TSCA has never included requirements for toxicity testing or generation of hazard data for new chemical substances prior to submission for review by EPA.

*Hazard Assessment*

Given the lack of toxicity testing requirements under TSCA, EPA only occasionally receives human health relevant hazard data for new chemical substances. EPA conducted an analysis of toxicity tests submitted to EPA from 2004 through 2012 for new chemical substances under TSCA and found that about 15% of the PMN submissions included some type of human health relevant hazard data; mostly animal tests for acute toxicity and irritation. TSCA provides EPA with the authority to require generation and submission of additional data when the information included with the PMN, coupled with that available to EPA risk assessors from prediction

modeling, read-across, internal archives, *etc.* is insufficient to permit a reasoned evaluation of the health and environmental effects of a new chemical substance. However, prior to making a request for testing using vertebrate animals, EPA must take into consideration reasonably available existing information, including toxicity information; computational toxicology and bioinformatics; and high-throughput screening methods and the prediction models of those methods (TSCA Section 4(h)(A)(i)-(iii)).

Given the historical lack of hazard data and the new requirements to consider reasonably available existing information, EPA has, for decades, relied on a number of approaches that do not rely on *de novo* toxicity testing, including computational toxicology (*e.g.*, predictive models and expert systems), analogue read-across (wherein available toxicity data for a chemical of similar structure and activity is used to assess the new chemical substance lacking data), and chemical categories (a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity) [ ADDIN EN.CITE <EndNote><Cite><Author>van Leeuwen</Author><Year>2009</Year><RecNum>14739</RecNum><DisplayText>[15]</DisplayText><record><rec-number>14739</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019290">14739</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>van Leeuwen, K.</author><author>Schultz, T. W.</author><author>Henry, T.</author><author>Diderich, B.</author><author>Veith, G. D.</author></authors></contributors><auth-address>TNO Quality of Life, Utrechtseweg 48, The Netherlands.</auth-address><titles><title>Using chemical categories to fill data gaps in

hazard assessment</title><secondary-title>SAR QSAR Environ Res</secondary-title><alt-title>SAR and QSAR in environmental research</alt-title></titles><periodical><full-title>SAR QSAR Environ Res</full-title><abbr-1>SAR and QSAR in environmental research</abbr-1></periodical><alt-periodical><full-title>SAR QSAR Environ Res</full-title><abbr-1>SAR and QSAR in environmental research</abbr-1></alt-periodical><pages>207-20</pages><volume>20</volume><number>3-4</number><edition>2009/06/23</edition><keywords><keyword>Hazardous Substances/pharmacology/*toxicity</keyword><keyword>*Quantitative Structure-Activity Relationship</keyword><keyword>Safety Management/*methods</keyword></keywords><dates><year>2009</year></dates><isbn>1026-776x</isbn><accession-num>19544189</accession-num><urls></urls><electronic-resource-num>10.1080/10629360902949179</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The integration of these methods with NAMs to advance testing strategies has been recognized by EPA [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ] and is consistent with the vision articulated in the 2007 report by the National Research Council in "Toxicity Testing in the 21st Century: A Vision and Strategy [ ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2007</Year><RecNum>14741</RecNum><DisplayText>[17]</DisplayText><record><rec-number>14741</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019531">14741</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>NRC</author></authors></contributors><titles><title>T

oxicity Testing in the 21st Century: A Vision and a Strategy, Washington, D.C. The National

Academies Press</title></titles><pages>216, DOI:

https://doi.org/10.17226/11970</pages><volume>ISBNs: Ebook: 978-0-309-13412-5;

Paperback: 978-0-309-15173-

3</volume><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].


*Dose-Response Analysis*

For assessing hazards to human health, EPA relies most heavily on read-across methods using an

analogue or a category of analogues to identify hazards and conduct dose-response analysis to

identify a point of departure (POD). While EPA has a number of existing "TSCA New

Chemicals Program (NCP) Chemical Categories" [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>14729</RecNum><

DisplayText>[3]</DisplayText><record><rec-number>14729</rec-number><foreign-

keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

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SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C.

20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-

title></periodical><pages>157, https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>201

0</year></dates><urls></urls></record></Cite></EndNote>], including for anionic, nonionic,

and cationic surfactants, the existing surfactant categories were developed and defined based

only on environmental toxicity considerations. Toxicity tests for analogues are used to identify a

point of departure (POD) (*i.e.,* a dose or concentration that marks the beginning of a low-dose

extrapolation) for assessing risks to the new chemical substance. This point can be the lower

bound on dose for an estimated incidence or a change in response level from a dose-response

model (*i.e.,* benchmark concentration or dose [BM(C)D], NOAE(C)L, LOAE(C)L, or human

equivalent concentration or dose [HE(C)D]) for an observed incidence or change in level of

response) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>14744</RecNum><

DisplayText>[18]</DisplayText><record><rec-number>14744</rec-number><foreign-

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timestamp="1596019975">14744</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B

enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, D.C. 20460</secondary-

title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection

Agency, Washington, D.C. 20460</full-title></periodical><pages>99,

https://www.epa.gov/sites/production/files/2015-

01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-

12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Once suitable analogues are identified, the strengths, limitations, and uncertainties associated with using the analogue as predictive of hazards of the new chemical substance are considered to derive a benchmark margin of exposure (MOE). The benchmark MOE is the result of multiplying all relevant uncertainty factors (UFs) to account for: (1) the variation in susceptibility among the members of the human population (*i.e.*, inter- individual or intraspecies variability); (2) the extrapolation from animal data to humans (*i.e.*, interspecies extrapolation); (3) the extrapolation from data in a study with less- than- lifetime exposure (*i.e.*, extrapolating from sub-chronic to chronic exposure); (4) the extrapolation from a LOAEL rather than from a NOAEL [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 20]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-

12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>2014</Year><RecNum>14742</RecNum><record><rec-number>14742</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019768">14742</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation</title><secondary-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>109, https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</pages><volume>EPA/R-14/002F</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. EPA prefers using existing information to develop data-derived extrapolation factors or chemical specific adjustment factors (DDEFs or CSAFs) rather than simply relying on defaults [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2014</Year><RecNum>14742</RecNum><DisplayText>[20]</DisplayText><record><rec-number>14742</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019768">14742</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>G uidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation</title><secondary-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>109, https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</pages><volume>EPA/R-14/002F</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote >]. This investigation includes a number of approaches to derive DDEFs to use in assessing new surfactant chemical substances.

*Exposure Assessment*

In assessing new chemical substances, EPA typically generates the human exposure estimates for workers using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as daily acute potential dose rates (PDRs) or lifetime average daily doses (LADDs). Given that new chemical substances will not have occupational exposure monitoring data, except for possible monitoring data on analogues, the PDR is typically used as an initial conservative exposure estimate when calculating the MOE.

Due to the surface-activity of surfactants at the point of exposure, the PDR is the appropriate dose-metric rather than the LADD which is typically used to assess cancer risks. For chemical substances used in a liquid, mist, or aerosol form, the general default PDR value is 1.875 mg/kg-

> **Commented [HT1]:** Mppd guidance

> **Commented [HT2]:** But why? Due to long term/chronic exposure?

> **Commented [HT3]:** Does this need more explaination? the PDR is mg/kg per day; so using repeated dose tox studies adjusted to # of days exposure. NOT using acute animal data
>
> Tala and Marc Odin comment: explain why PDDR is appropriate

[PAGE ]

bw/day for inhalable aerosols or 0.625 mg/kg-bw/day for respirable aerosols calculated using the

default values as shown in [ REF _Ref46930162 \h \* MERGEFORMAT ] [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2015</Year><RecNum>14745</RecNum><

DisplayText>[21]</DisplayText><record><rec-number>14745</rec-number><foreign-

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timestamp="1596021217">14745</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>C

hemSTEER User Guide, Chemical Screening Tool for Exposures and Environmental

Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental

Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-

title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency,

Washington, D.C. 20460</full-title></periodical><pages>403,

https://www.epa.gov/sites/production/files/2015-

05/documents/user_guide.pdf</pages><dates><year>2015</year></dates><urls></urls></recor

d></Cite></EndNote>].

**Table [ SEQ Table \* ARABIC ].** Default values used for calculating the PDR.

| Description | Equation | Description | Equation[a] | Defaults | Units |
|---|---|---|---|---|---|
| PDR (mg/kg-bw/day) | I/BW | Inhalation PDR (I) | $Cm \times b \times h$, where Cm is the mass concentration of chemical in air, b is the volumetric inhalation rate ($0 < b \leq 7.9$), and h is the exposure duration ($0 \leq h \leq 24$) | $Cm = 15\ mg/m^3$<br><br>$b = 1.25\ m^3/hr$<br><br>$h = 8\ hours/day$ | mg/day |
| | | Body weight (BW) | BW ($0 \leq BW$) | 80 kg-bw | kg-bw |

[a] Cm may also be adjusted for the mass concentration of the chemical with a PEL in air (based on OSHA PEL – TWA; default = 15 mg/m$^3$ inhalable; 5 mg/m$^3$ for respirable, the weight fraction of chemical in particulate (Ys) ($0 < Ys \leq 1$), the weight fraction of chemical or metal with a PEL in particulate (Ypel) ($0 < Ypel \leq 1$) using the following equation: $Cm = KCk \times Ys/Ypel$

[PAGE ]

The PDR is calculated using a default worker values of 8 hrs/day and 5 days/week, unless chemical-specific manufacture, processing or use information are provided in the PMN. The exposure regimen used in animal studies often do not reflect occupational exposure scenarios, such that a duration adjustment and a dosimetric factor (*i.e.,* RDDR value) is applied to the POD from the animal study to derive human equivalent concentrations (HECs) exposed human population. While this adjustment would optimally be made using physiologically-based pharmacokinetic model [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]; the data required to conduct such modelling rarely exist for new chemical substances.

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Therefore, occupational exposures are adjusted using particle deposition models with human exertion (work) ventilation rates and exposure durations appropriate to the particular occupational setting and chemical use scenario.

*Risk Characterization*

Risk characterization is an integral component of the risk assessment process for both ecological and health risks, *i.e.*, it is the final, integrative step of risk assessment. As defined in EPA's Risk Characterization Policy, the risk characterization integrates information from the hazard and exposure components of the risk assessment and synthesizes an overall conclusion about risk that is complete, informative, and useful for decision-making. A risk characterization conveys the risk assessor's judgment as to the nature and existence of (or lack of) human health or ecological risks [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2000</Year><RecNum>14747</RecNum><DisplayText>[23]</DisplayText><record><rec-number>14747</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021806">14747</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Risk Characterization</title><secondary-title>Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>189,

https://nepis.epa.gov/Exe/ZyPDF.cgi/40000006.PDF?Dockey=40000006.PDF</pages><volume>EPA 100-B-00-002</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>].
As noted in EPA's Risk Characterization Handbook "Risk characterization at EPA assumes different levels of complexity depending on the nature of the risk assessment being characterized. The level of information contained in each risk characterization varies according to the type of assessment for which the characterization is written and the audience for which the characterization is intended."

Under TSCA section 5, EPA must determine whether a chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use. EPA generally uses an MOE approach to characterize risks of new chemical substances as a starting point to estimate non-cancer risks for acute and chronic exposures. The MOE is the HEC derived from a POD for a specific health endpoint (from hazard assessment) divided by the exposure concentration for the specific scenario of concern (from exposure assessment). To determine whether the resulting MOE results in an adequate margin between human exposure estimates and the HEC derived from a POD, the MOE value is compared with a benchmark MOE. When using MOEs as risk estimates for non-cancer health effects, the benchmark MOEs are used to interpret the risk estimates. Generally, when the MOE is less than the benchmark MOE human health risks are interpreted as possible. On the other hand, negligible concerns would be expected if the MOE exceeds the benchmark MOE. The MOE approach is a widely recognized point estimate method and allows for providing a risk profile for a range of different non-cancer health effects and different exposure scenarios.

[PAGE ]

In summary, to conduct a risk evaluation for new chemical substances, as required under TSCA section 5, EPA conducts a hazard assessment, using empirical data when available, but most often using analogues, to identify a POD(s) and to develop a benchmark MOE that reflects specific uncertainties associated with data available for use in the evaluation. This hazard assessment is combined with the exposure assessment, to calculate an MOE, which is compared to the benchmark MOE to determine whether risks are identified. The risk characterization is used to inform the "unreasonable risk" determination.

## RESULTS AND DISCUSSION

### Literature Search and Screening Results

The initial PubMed search identified 594 articles that were subjected to title and abstract screening. Of these, 551 did not meet the PECO criteria, whereas 43 met the PECO criteria and were selected for full text review. An additional 17 references were included for full text review that met the PECO criteria and were identified through additional search strategies, screening gray literature, references for other types of chemical substances, *etc*. Of the 60 articles evaluated through full text screening, 16 were identified as relevant and carried forward in the present evaluation, whereas the remaining 44 studies were excluded because they lacked relevant information on respiratory tract effects or presented inconclusive epidemiology findings. In the supplemental literature search, 1242 studies were identified on PubMed and Embase (combined). Following title and abstract screening, 1217 of these studies were excluded because they did not meet the PECO criteria. A total of 35 studies met the PECO criteria and were selected for full text screening, which

resulted in 25 studies that were identified for review and 10 studies that were deemed irrelevant and excluded. Of the 25 studies identified for review, 15 of the studies were identified in the initial literature search.

The information identified in the systematic review was used to inform the section on Category Boundaries and subcategories with the boundaries, to summarize the health effects of surfactants under the section on Hazard Identification, and to identify potential NAMs for use in the section on Tiered-Testing Strategies.

**Category Boundaries**

The following structural and functional criteria (hereinafter referred to as the "Surfactant Criteria") are used to distinguish chemical substances, which include polymers and UVCB substances,[1] intended for use as surfactants from other amphiphilic compounds (*e.g.*, ethanol) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]:

1. A substance which has surface-active properties, and which consists of one or more hydrophilic and one or more hydrophobic groups;

2. The substance must be capable of reducing the surface tension between air and water to 45 milliNewtons/meter (mN/m) or below at a test condition of 0.5 wt% in water and a temperature of 20°C (*Cf.* Pure water has a surface tension of 72.8 mN/m at 20°C); and

---

[1] Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB Substance)

3. The substance self-associates in water to form micellar or vesicular aggregates at a concentration of 0.5 wt% or below.

The Surfactants Category is further defined into three general subcategories including nonionic, anionic, and cationic substances. Within these subcategories, The Surfactant Category is subcategorized for those chemical substances that initially meet the Surfactant Criteria and possess ionic or nonionic properties, as discussed below. Note, though not listed in the following subcategories, amphoteric chemical substances that meet the Surfactant Criteria would also be included within these subcategories (*i.e.*, cationic or anionic surfactants), depending on their pH. Lung lining fluids are near neutral pH, with various measurements ranging from 6.6 to 7.1 [ ADDIN EN.CITE   ADDIN EN.CITE.DATA   ]. The pKa for each component of an amphoteric surfactant should be considered within this pH range and the assessment should be conducted on the predominant components. The non-ionized fraction for acids/bases should be calculated as follows:

Acids Fraction$_{non-ionized}$ = 1 / (1 + 10$^{pH-pKa}$)

Bases Fraction$_{non-ionized}$ = 1 / (1 + 10$^{pKa-pH}$)

Where the pH represents the physiological pH in the lung (*i.e.*, 6.6 to 7.1), and the pKa represents the value for the respective component (*e.g.*, carboxylic acid or amine).

Nonionic surfactants are identified as any neutral chemical substance that meets the Surfactant Criteria. Common nonionic surfactants include alkylphenol chemical substances with one or more than one ethoxylate (EO) unit as well as linear and branched alcohol chemical substances with one or more EO units. For example, octylphenoxypolyethoxyethanol, a common nonionic octylphenol EO surfactant, and Polysorbate 80 (or Tween 80), another nonionic alkyphenol ethoxylate with increased alkyl chain length and number of EO units, are shown in [ REF _Ref46930277 \h \* MERGEFORMAT ]. The surface tensions of octylphenoxypolyethoxyethanol and Polysorbate 80 range from 30-31 mN/m to 37.96 mN/m, respectively ([ REF _Ref46930277 \h \* MERGEFORMAT ]) [ ADDIN EN.CITE <EndNote><Cite><Author>Kothekar</Author><Year>2007</Year><RecNum>14758</RecNum><DisplayText>[30]</DisplayText><record><rec-number>14758</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025228">14758</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kothekar, S.C.</author><author>Ware, A.M.</author><author>Waghmare, J.T.</author><author>Momin, S.A.</author></authors></contributors><titles><title>Comparative Analysis of the Properties of Tween-20, Tween-60, Tween-80, Arlacel-60, and Arlacel-80</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>477-484, https://www.tandfonline.com/doi/abs/10.1080/01932690601108045</pages><volume>28</volume><number>3</number><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].

Anionic surfactants were identified as any chemical substance with a net negative charge that meets the Surfactant Criteria (*e.g.*, alkyl sulfonates, alkylbenzene sulfonates, alkylether sulfates, alkyl silicic acids, alkyl phosphates, alkyl carboxylic acids, or combinations of these anionic groups). The surface tension of SDS is reported to be 35 mN/m ([ REF _Ref46930277 \h \* MERGEFORMAT ]).

Cationic surfactants are identified as any chemical substance with a net positive charge that meets the Surfactant Criteria (*e.g.*, alkylammonium chlorides and benzalkonium chlorides). DDAC is a a representative member of this subcategory, although as noted previously, it also possesses biocidal properties. The surface tension of DDAC is reported to be 27.61 mN/m ([ REF _Ref46930277 \h \* MERGEFORMAT ]).

**Commented [ST5]:** "The [ HYPERLINK "https://en.wikipedia.org/wiki/Critical_micelle_concentration" \o "Critical micelle concentration" ] (CMC) in pure water at 25 °C is 8.2 mM,[ HYPERLINK "https://en.wikipedia.org/wiki/Sodium_dodecyl_sulfate" \l "cite_note-CMC-1" ] and the [ HYPERLINK "https://en.wikipedia.org/wiki/Aggregation_number" \o "Aggregation number" ] at this concentration is usually considered to be about 62.[ HYPERLINK "https://en.wikipedia.org/wiki/Sodium_dodecyl_sulfate" \l "cite_note-3" ] The [ HYPERLINK "https://en.wikipedia.org/wiki/Micelle" \o "Micelle" ] ionization fraction (α) is around 0.3 (or 30%).[ HYPERLINK "https://en.wikipedia.org/wiki/Sodium_dodecyl_sulfate" \l "cite_note-Barney_L-4" ]"

[ HYPERLINK "http://hera.ugr.es/doi/15008447.pdf" ] this paper shows ST to be a lot higher

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Table [ SEQ Table \* ARABIC ]. Example Chemicals that Meet "Surfactant Criteria" and Nonionic, Anionic and Cationic Subcategorization.

| Nonionic Surfactants | | | | | |
|---|---|---|---|---|---|
| Chemical Name in Text | Other Relevant Names | Criteria 1 | | Criteria 2 | Criteria 3 |
| | | Hydrophobic group(s) | Hydrophilic group(s) | Surface Tension | Critical Micelle Concentration (CMC) |
| Octoxynol 9<br><br>CASRN 9002-93-1 | Triton X-100<br><br>Octylphenol ethoxylate<br><br>CAS Name: Poly(oxy-1,2-ethanediyl), .alpha.-[4-1,1,3,3-tetramethylbutyl)phenyl]-.omega.-hydroxy | octylphenol group | polyoxyethylene (9) unit | ~30.5 mN/m at 5 g/L (0.5 wt%) and 25°C* [ ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sch | 0.17 g/L or 0.01 wt% [ ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal |

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| Tyloxapol<br><br>Defomaire<br><br>Alevaire<br><br>CASRN 25301-02-4 | CAS Name: Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol | multiple octyl phenol groups | multiple polyoxyethylene (9) units | ~37 mN/m at 5 g/L (0.5 wt%) and 25°C* [ ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db- | 0.038 g/L or 0.0038 wt% [ ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign- |

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| Polyoxyethylene-10-oleyl ether<br><br>$C_{18:1}E_{10}$<br><br>Oleyl ethoxylate | | oleyl group | polyoxyethylene (10) unit | 35.17 mN/m at $4\times10^5$ M (0.028%) and 25°C* [ ADDIN EN.CITE | $4\times10^{-5}$ M or 0.028 wt % at 25°C [ ADDIN EN.CITE <EndNote><Cite>< |

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| CASRN 9004-98-2 | CAS Name: Poly(oxy-1,2-ethanediyl), .alpha.-(9Z)-9-octadecen-1-yl-.omega.-hydroxy | | | &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Liu&lt;/Author&gt;&lt;Year&gt;2006&lt;/Year&gt;&lt;RecNum&gt;14761&lt;/RecNum&gt;&lt;DisplayText&gt;[32]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;14761&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025582"&gt;14761&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Liu, F.&lt;/author&gt;&lt;author&gt;Wang, Z.&lt;/author&gt;&lt;author&gt;Sun, D.&lt;/author&gt;&lt;author&gt;Wei, X.&lt;/author&gt;&lt;author&gt;Zhou, W.&lt;/author&gt;&lt;author&gt;Li, G.&lt;/author&gt;&lt;author&gt;Zhang, | Author&gt;Liu&lt;/Author&gt;&lt;Year&gt;2006&lt;/Year&gt;&lt;RecNum&gt;14761&lt;/RecNum&gt;&lt;DisplayText&gt;[32]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;14761&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025582"&gt;14761&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Liu, F.&lt;/author&gt;&lt;author&gt;Wang, Z.&lt;/author&gt;&lt;author&gt;Sun, D.&lt;/author&gt;&lt;author&gt;Wei, X.&lt;/author&gt;&lt;author&gt;Zhou, W.&lt;/author&gt;&lt;autho |
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| Polyoxyethylene-10-dodecyl ether<br><br>CASRN: 9002-92-0 | $C_{12}E_{10}$<br><br>Polyoxyethylene (10) lauryl ether<br><br>CAS Name: Poly(oxy-1,2-ethanediyl),-.alpha.-dodecyl-.omega.- | dodecyl group | polyoxyethylene (10) unit | C12E9: 36 mN/m at 23°C*<br><br>C12E12: 32 mN/m at 23°C* [ ADDIN EN.CITE <EndNote><Cite><Author>Rosen</Author><Year>1989</Year><RecNum>14763</RecNum><DisplayText>[33]</DisplayText><record><rec-number>14763</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026543">14763</key></foreign-keys><ref-type name="Edited Book">28</ref-type><contributors><authors><author>Rosen, M.J.</author></authors></contributors><titles><title>Surfactant | $12.7\times10^{-6}$ M or 0.0008 wt% at 30°C [ ADDIN EN.CITE <EndNote><Cite><Author>Sulthana</Author><Year>2000</Year><RecNum>14762</RecNum><DisplayText>[34]</DisplayText><record><rec-number>14762</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025808">14762</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sulthana, S.B.</author><author>Rao, |

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Also, C12E9 at $1\times10^{-6}$ M at 23°C and C12E12 at $1.4\times10^{-6}$ M at 23°C [ ADDIN EN.CITE <EndNote><Cite><Author>Rosen</Author><Year>1989</Year><RecNum>14763</RecNum><DisplayText>[33]</DisplayText><record><rec-number>14763</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026543">14763</key></foreign-keys><ref-type name="Edited |

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| | | | | | Book">28</ref-type><contributors><authors><author>Rosen, M.J.</author></authors></contributors><titles><title>Surfactants and interfacial phenomena</title></titles><pages>431,</pages><dates><year>1989</year></dates><pub-location>New York</pub-location><publisher>John Wiley &amp; Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>] |
| Polysorbate 20 or Tween 20 CASRN 9005-64-5 | Polyoxyethylene (20) sorbitan monolaurate CAS Name: Sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl) derivs. | dodecanoyl group | sorbitan polyoxyethylene (20) unit | 38 mN/m at $8.04 \times 10^{-5}$ M (0.001%) and 21°C* [ ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2001</Year><RecNum>14756</RecNum><DisplayTex | $8.04 \times 10^{-5}$ M or 0.001 wt% at 21°C [ ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2001</Year><RecNum>147 56</RecNum><DisplayText>[35]</Dis |

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| | | | | t>[35]</DisplayText ><record><rec-number>14756</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre 0azr5evearxfds0err5s r" timestamp="1596024 348">14756</key></ foreign-keys><ref-type name="Journal Article">17</ref-type><contributors>< authors><author>Ki m, C.</author><author> Hsieh, Y.-L.</author></authors ></contributors><titl es><title>Wetting and absorbency of nonionic surfactant solutions on cotton fabrics</title><secon dary-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</secondary-title></titles><period ical><full- | playText><record> <rec-number>14756</re c-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0z re0azr5evearxfds0e rr5sr" timestamp="15960 24348">14756</ke y></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors ><authors><author >Kim, C.</author><author >Hsieh, Y.-L.</author></autho rs></contributors>< titles><title>Wettin g and absorbency of nonionic surfactant solutions on cotton fabrics</title><seco ndary-title>Colloids and Surfaces A: Physicochemical and Engineering |

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| | | | | title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>385-397</pages><volume>187-188</volume><number>31</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>] | Aspects</secondary-title></titles><periodical><full-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>385-397</pages><volume>187-188</volume><number>31</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>] |
|---|---|---|---|---|---|
| Polysorbate 80 or<br><br>Tween 80<br><br>CASRN 9005-65-6 | Polyoxyethylene (20) sorbitan monooleate<br><br>CAS Name: Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) derivs. | octadecenoyl group | sorbitan polyoxyethylene (20) unit | 37.96 mN/m at 5 g/L (0.5 wt %) and 30°C [ ADDIN EN.CITE <EndNote><Cite><Author>Kothekar</Author><Year>2007</Year><RecNum>14758</RecNum><DisplayText>[30]</DisplayText><record><rec-number>14758</rec-number><foreign-keys><key app="EN" | $1.5\times10^{-5}$ M or 0.{ **Commented [HT11]:** g/L?? wt% at 25°C [ ADDIN EN.CITE <EndNote><Cite><Author>Mahmood</Author><Year>2013</Year><RecNum>14757</RecNum><DisplayText>[36]</DisplayText><record><rec-number>14757</rec- |

| | | | | db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025228">14758</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kothekar, S.C.</author><author>Ware, A.M.</author><author>Waghmare, J.T.</author><author>Momin, S.A.</author></authors></contributors><titles><title>Comparative Analysis of the Properties of Tween-20, Tween-60, Tween-80, Arlacel-60, and Arlacel-80</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><period | number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024783">14757</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mahmood, M.E.</author><author>Al-Koofee, D.A.F.</author></authors></contributors><titles><title>Effect of Temperature Changes on Critical Micelle Concentration for Tween Series Surfactants</title><secondary-title>Global Journal of Science Frontier Research Chemistry</secondary-title></titles><perio |

| | | | | ical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>477-484, https://www.tandfonline.com/doi/abs/10.1080/0193269060110 8045</pages><volume>28</volume><number>3</number><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>] | dical><full-title>Global Journal of Science Frontier Research Chemistry</full-title></periodical><pages>5, https://journalofscience.org/index.php/GJSFR/article/view/816/681</pages><volume>13(B)</volume><number>4</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>] |
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| Poloxamer 188 <br><br> CASRN 691397-13-4 | CAS Name: Oxirane, 2-methyl-, polymer with oxirane, triblock | polyoxypropylene (27) unit | two polyoxyethylene (80) units | ~42-44 mN/m at ~0.5 wt% and 36°C [ ADDIN EN.CITE ADDIN EN.CITE.DATA ] | $4.8 \times 10^{-4}$ M or 0.4 wt% at 37°C [ ADDIN EN.CITE ADDIN EN.CITE.DATA ] |
| N,N-Dimethyl-dodecylamine-N-oxide*** <br><br> CASRN 1643-20-5 | Lauryl dimethylamine oxide <br><br> CAS Name:1-Dodecanamine, N,N-dimethyl-, N-oxide | dodecyl group | amine oxide unit | 34.1 mN/M at 1 g/L (0.1 wt.%) and 20°C [ ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14772</RecNum><Display | $1.7 \times 10^{-3}$ M or 0.039 wt% [ ADDIN EN.CITE <EndNote><Cite><Author>Hoffmann</Author><Year>1990</Year><RecNum>14764</RecNu |

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| | | | | Text>[39]</DisplayText><record><rec-number>14772</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596028055">14772</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Dodecyldimethylamine oxide, CASRN: 1643-20-5, EC number: 216-700-6, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals | m><DisplayText>[40]</DisplayText><record><rec-number>14764</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026736">14764</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hoffmann, H.</author></authors></contributors><titles><title>Correlation between surface and interfacial tensions with micellar structures and properties of surfactant solutions</title><secondary-title>Progress in |

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| | | | | Agency</full-title></periodical><p ages>https://echa.eur opa.eu/registration-dossier/-/registered-dossier/10062/4/11</ pages><dates><year >2020</year></dates ><urls></urls></reco rd></Cite></EndNot e>] | Colloid &amp; Polymer Science</secondary -title></titles><perio dical><full-title>Progress in Colloid &amp; Polymer Science</full-title></periodical>< pages>16-28, https://link.springer .com/chapter/10.10 07%2FBFb011623 8</pages><volume >18</volume><dat es><year>1990</ye ar></dates><urls>< /urls></record></Ci te></EndNote>]<br><br>$1\times10^{-5}$ M to 5.5x10-5 M at 2...[ ADDIN EN.CITE <EndNote><Cite>< Author>Mukerjee</ Author><Year>197 1</Year><RecNum >14765</RecNum> <DisplayText>[41] </DisplayText><re cord><rec-number>14765</re |
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| | | Criteria 1 | | Criteria 2 | Criteria 3 |
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| | | | | | NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>] |
| **Anionic Surfactants** | | | | | |
| **Chemical Name in Text** | **Other Relevant Names** | **Hydrophobic group(s)** | **Hydrophilic group(s)** | **Surface Tension** | **Critical Micelle Concentration (CMC)** |

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| Sodium dodecyl sulfate<br><br>CASRN: 151-21-3 | SDS<br><br>CAS Name: Sulfuric acid monododecyl ester sodium salt (1:1) | dodecyl group | sulfate group | 35 mN/m at 0.29% (wt%) and 20°C [ | $8.25\times10^{-3}$ M or 0.24 wt% at 20°C [ |
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35 mN/m at 0.29% (wt%) and 20°C [

ADDIN EN.CITE <EndNote><Cite><Author>Hernainz</Author><Year>2002</Year><RecNum>14768</RecNum><DisplayText>[42]</DisplayText><record><rec-number>14768</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027363">14768</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hernainz, F.</author><author>Caro, A.</author></authors></contributors><titles><title>Variation of surface tension in aqueous solutions of sodium dodecyl

$8.25\times10^{-3}$ M or 0.24 wt% at 20°C [

ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Crit

| | | | | sulfate in the flotation batch</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</secondary-title></titles><periodical><full-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>19-24, https://www.sciencedirect.com/science/article/abs/pii/S0927775701005751</pages><volume>196</volume><number>1</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] | ical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dat |

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| | | | | | es><year>1971</year></dates><urls></urls></record></Cite></EndNote>] |
| Oleoyl sarcosine<br><br>CASRN 110-25-8 | CAS Name: Glycine, N-methyl-N-((9Z)-1-oxo-9-octadecen-1-y | oleyl group | carboxylic acid anion | 31.91 mN/M at (0.1% wt%) at 19.9°C** [ ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14767</RecNum><DisplayText>[43]</DisplayText><record><rec-number>14767</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027202">14767</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-methyl-N-(1- | 2.6×10⁻³ wt% temperature not reported, assumed to be room temperature ~25°C [ ADDIN EN.CITE <EndNote><Cite><Author>ChattemChemicals</Author><Year>2020</Year><RecNum>14769</RecNum><DisplayText>[44]</DisplayText><record><rec-number>14769</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027596">14769</key></foreign-keys><ref-type name="Journal Article">17</ref- |

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| | | | | oxo-9-octadecenyl)aminoac etate, CASRN 3624-77-9, EC number: 222-829-9, Surface Tension</title><seco ndary-title>European Chemicals Agency</secondary-title></titles><period ical><full-title>European Chemicals Agency</full-title></periodical><p ages>https://www.ec ha.europa.eu/fi/web/g uest/registration-dossier/-/registered-dossier/5350/4/11</p ages><dates><year> 2020</year></dates> <urls></urls></recor d></Cite></EndNote >]<br><br>**Note this reference is to the sodium salt. | type><contributors ></authors><author >ChattemChemical s</author></author s></contributors><t itles><title>Oleoyl Sarcosine, CASRN 110-25-8</title><secondary -title>Product Information</secon dary-title></titles><perio dical><full-title>Product Information</full-title></periodical>< pages>https://www. chattemchemicals.c om/</pages><dates ><year>2020</year ></dates><urls></u rls></record></Cite ></EndNote>]<br><br>**Note this reference is to the sodium salt. |
| Sodium lauroyl sarcosinate<br><br>CASRN: 137-16-6 | CAS Name: Glycine, N-methyl-N-(1-oxododecyl)-, sodium salt (1:1) | lauryl group | carboxylic acid anion | 40.5 mN/m at 2% w/w (█ wt%) and 20°C [ ADDIN EN.CITE <EndNote><Cite><A | $8.0 \times 10^{-2}$ wt%<br><br>Reference? Wayne's |

Commented [HT18]: Really wt% or M
If wt% for consistency change to 0.08 wt%

Commented [HT17]: Assume w/w was as reported...what would be wt%?

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| | | | | uthor>Dossier</Author><Year>2020</Year><RecNum>14770</RecNum><DisplayText>[45]</DisplayText><record><rec-number>14770</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027817">14770</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-lauroylsarcosinate, CASRN 137-16-6, EC number: 205-281-5, Surface Tension</title><secondary-title>European Chemicals Agency</secondary- | |

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| Dioctyl Sulfosuccinate Sodium Salt<br><br>CASRN: 577-11-7 | DOSS<br><br>Dioctyl sodium sulfosuccinate<br><br>CAS Name: Butanedioic acid, 2-sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt | two 2-ethyl hexyl groups | sulfosuccinate group | <28 mN/m at 0.5 vol% and 25°C* [ ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>1957</Year><RecNum>14755</RecNum><DisplayText>[46]</DisplayText><record><rec-number>14755</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024 | 6.8×10⁻⁴ M or 0 wt% at 25°C [ ADDIN EN.CIT <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0e |

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| | | | | 180">14755</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, E.F.</author><author>Woodberry, N.T.</author><author>Dixon, J.K.</author></authors></contributors><titles><title>Purification and surface tension properties of alkyl sodium sulfosuccinates</title><secondary-title>Journal of Colloid Science</secondary-title></titles><periodical><full-title>Journal of Colloid Science</full-title></periodical><pages>452-459</pages><volume>12</volume><number>5</number><dates><year>1957</year | rr5sr" timestamp="159602 6897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared |

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| | | ></dates><urls></url s></record></Cite></ EndNote>] | under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical>< pages>242, https://nvlpubs.nist. gov/nistpubs/Legac y/NSRDS/nbsnsrds 36.pdf</pages><dat es><year>1971</ye ar></dates><urls>< /urls></record></Ci te></EndNote>] |
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| Cationic Surfactants | | | | |
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| Chemical Name in Text | Other Relevant Names | Criteria 1 | | Criteria 2 | Criteria 3 |
|---|---|---|---|---|---|
| | | Hydrophobic group(s) | Hydrophilic group(s) | Surface Tension | Critical Micelle Concentration (CMC) |
| Benzalkonium chloride  CASRN: 8001-54-5 | CAS Name:  Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides | alkyl chains are C12, C14, C16 and C18 and benzyl group | quaternary nitrogen | 37 mN/m at concentrations greater than about $4\times10^{-4}$M and 25°C* [ ADDIN EN.CITE <EndNote><Cite><A | C12: reported values range from 2.3 - $8.5\times10^{-3}$ M or 0.078 - 0.29 wt% at 25°C |

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| | | | | uthor>Nandni</Author><Year>2013</Year><RecNum>14766</RecNum><DisplayText>[47]</DisplayText><record><rec-number>14766</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027033">14766</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nandni, D.</author><author>Mahajan, R.K.</author></authors></contributors><titles><title>Micellar and Interfacial Behavior of Cationic Benzalkonium Chloride and Nonionic Polyoxyethylene Alkyl Ether Based | C14: $3.7 \times 10^{-4}$ M or 0.014 wt%  $\quad$ Commented [HT24]: also at 23 C? <br><br>C16: $4.2 \times 10^{-5}$ M or 0.0016 wt% at 23°C <br><br><br>C18: reported values range from 7.1 - $8.5 \times 10^{-6}$ M or 0.0003 - 0.00036 wt% at 23°C [ ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="15960 |

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| | | | | Mixed Surfactant Systems</title><secondary-title>Journal of Surfactants and Detergents</secondary-title></titles><periodical><full-title>Journal of Surfactants and Detergents</full-title></periodical><pages>587-599, https://doi.org/10.1007/s11743-012-1427-z</pages><volume>16</volume><number>4</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>] | 26897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of |
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| | | | | | Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>] |
| Didecyldimethyl ammonium chloride<br><br>CASRN 7173-51-5 | DDAC<br><br>CAS Name: 1-Decanaminium, N-decyl-N,N-dimethyl-, chloride (1:1) | decyl groups | quaternary nitrogen | 25.82 mN/m at 1 g/L (0.1 wt%) and 20°C [ ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14771</RecNum><DisplayText>[48]</DisplayText><record><rec-number>14771</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5s | 0.39 g/L or 0.039 wt% at 25°C [ ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14771</RecNum><DisplayText>[48]</DisplayText><record><rec-number>14771</rec-number><foreign-keys><key app="EN" db- |

| | | | | r" timestamp="1596027946">14771</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/5864/4/11</pages><dates><year>2020</year></dates> | id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027946">14771</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa. |
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*Not all of the surface tension measurement references identified are run at exactly 20 °C, but they are sufficiently close (within 5 °C) so as not to affect the measurement. In addition, several measurements were run at 0.1% instead of the recommended 0.5%. Increasing the concentration to 0.5% is likely to lower the surface tension.

**Commented [HT25]:** Any reference for this?

**Carboxylic acid compounds, such as oleoyl sarcosine, have a carboxyl group pKa value of ~5, thus at physiological pH values maintained near 7 in the lung, the carboxyl group will be 99% in the anionic form according the Henderson-Hasselbalch equation. Since sodium is the major cation in mammalian body fluids (~145 mM), the use of the sodium oleoyl sarcosine surface tension value is appropriate for its characterization.

***Zwitterionic: At pH 7, 90% expected to be nonionic; only small amount cationic.

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**Hazard Identification**

There is concern for dysfunction of natural surfactant in the lung from inhalation of surfactants. Additionally, there is evidence that some surfactants or similar structures may also interfere with the cell membrane [ ADDIN EN.CITE ADDIN EN.CITE.DATA ]. The capacity of exogenous surfactants to interfere with pulmonary surfactant and impair pulmonary function has been demonstrated in human volunteers and in laboratory animals. The pulmonary response to surfactant aerosol is likely in proportion to the exposure concentration and duration, but available data on acute and repeated-dose effect levels are limited within each subcategory, which limits establishing a correlation between chemical properties and exposure methods (*e.g.*, aerosol droplet size) and toxicity.

Nonionic Surfactants

*In Vivo Studies*

Several studies were identified for the nonionic siliconized superinone respiratory detergent, formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol (CASRN 25301-02-4; also known as Defomarie, Alevaire, Tyloxapol). Healthy human volunteers showed significantly decreased pulmonary compliance following acute inhalation of Defomaire beyond that produced by the distilled water control [ ADDIN EN.CITE <EndNote><Cite><Author>Obenour</Author><Year>1963</Year><RecNum>13656</RecNum><DisplayText>[51]</DisplayText><record><rec-number>13656</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1479320595">13656</key></foreign-keys><ref-type name="Journal

Article">17</ref-type><contributors><authors><author>Obenour, R. A.</author><author>Saltzman, H. A.</author><author>Sieker, H. O.</author><author>Green, J. L.</author></authors></contributors><titles><title>Effects of surface-active aerosols and pulmonary congestion on lung compliance and resistance</title><secondary-title>Circulation</secondary-title><alt-title>Circulation</alt-title></titles><periodical><full-title>Circulation</full-title><abbr-1>Circulation</abbr-1></periodical><alt-periodical><full-title>Circulation</full-title><abbr-1>Circulation</abbr-1></alt-periodical><pages>888-92</pages><volume>28</volume><edition>OBENOUR, R A&#xD;SALTZMAN, H A&#xD;SIEKER, H O&#xD;GREEN, J L&#xD;1963/11/01</edition><keywords><keyword>Aerosols</keyword><keyword>Alcohols</keyword><keyword>Ethanol</keyword><keyword>Heart Failure</keyword><keyword>Humans</keyword><keyword>Infusions, Parenteral</keyword><keyword>Injections, Intravenous</keyword><keyword>Lung</keyword><keyword>Lung Compliance</keyword><keyword>Pulmonary Edema</keyword><keyword>Respiratory Function Tests</keyword><keyword>Silicones</keyword><keyword>Sodium Chloride</keyword><keyword>Surface-Active Agents</keyword></keywords><dates><year>1963</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0009-7322 (Print)&#xD;0009-7322 (Linking)</isbn><accession-num>14079193</accession-num><call-num>0 (Aerosols)&#xD;0 (Alcohols)&#xD;0 (Silicones)&#xD;0 (Surface-Active Agents)&#xD;3K9958V90M (Ethanol)&#xD;451W47IQ8X (Sodium Chloride)</call-num><urls></urls><remote-database-provider>NLM</remote-database-

provider><language>Eng</language></record></Cite></EndNote>].    Increased    minimum

surface tension due to detergent was demonstrated, and shown to be dose-dependent, using

pulmonary surfactant extracted from dogs and mixed *in vitro* with the nonionic surfactant

tyloxapol (Alevaire) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. *In vivo* exposure of dogs

to Alevaire in this study (8 h aerosol exposure; vehicle and concentration not reported) produced

little effect (only 1/10 dogs exposed to Alevaire showed increased minimum surface tension),

which the authors concluded support the dose-dependence of the effect and indicate that small

amounts of detergent can be present in the lungs without detectably altering surfactant function [

ADDIN EN.CITE    ADDIN EN.CITE.DATA    ].

Other pulmonary effects in dogs and/or sheep exposed to nonionic surfactant, tyloxapol, included

reduced oxygen content of arterial blood (*i.e.*, impaired gas exchange in the lung), increases in

pulmonary extravascular water volume and wet-to-dry weight ratio of the lungs, and grossly

visible pulmonary edema and atelectasis (*i.e.,* collapsed alveoli) [ ADDIN EN.CITE    ADDIN

EN.CITE.DATA    ]. In the study by Modell *et al.* (1969) [ ADDIN EN.CITE    ADDIN

EN.CITE.DATA    ], no gross pathology differences were seen in detergent-exposed vs. control

lungs of dogs, although some portions of both control and exposed lungs were heavy and

discolored reddish-purple, which may have been caused by fluid accumulation from the liquid

aerosol exposures and/or the use of hypotonic saline in the study (0.45% NaCl). Normal

appearances were observed in the remaining areas of the lungs.

In rodent models, irritation and inflammatory effects on the respiratory tract has been observed

with varying degrees of severity. Acute inhalation exposure to Polysorbate 20, which is not

irritating to the skin or eyes [ ADDIN EN.CITE
<EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14776</RecNum
><DisplayText>[52]</DisplayText><record><rec-number>14776</rec-number><foreign-
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6.5 moles ethoxylated, CASRN: 9005-64-5, EC number: 500-018-3, Skin
irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-
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title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-
dossier/13525/7/4/2</pages><dates><year>2020</year></dates><urls></urls></record></Cite>
</EndNote>], via nose-only administration for 4 hours in Wistar Han rats to a concentration of 5.1

mg/L (5,100 mg/m$^3$, MMAD 2.2 μm, GSD 2μm) did not observed an increase in mortalities,

clinical signs, or abnormalities in the gross pathology [ ADDIN EN.CITE
<EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14777</RecNum
><DisplayText>[53]</DisplayText><record><rec-number>14777</rec-number><foreign-
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Article">17</ref-type><contributors><authors><author>Registration
Dossier</author></authors></contributors><titles><title>Sorbitan monolaurate, ethoxylated 1 -
6.5 moles ethoxylated, CASRN: 9005-64-5, EC number: 500-018-3, Acute Toxicity:
Inhalation</title><secondary-title>European Chemicals Agency</secondary-

title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/13525/7/3/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. The total lung deposition mass was calculated to be $6.6 \times 10^4 \mu g$ using MPPD modeling. A respiratory irritation study on a mixture containing octylphenoxypolyethoxyethanol [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ], which can be severely irritating to the skin and eyes in male Webster mice using the ASTM Method E981 where animals were exposed for 3 hours to concentrations of 12, 22, 51, 118, and 134 $mg/m^3$ and allowed 30-60 minutes recovery time observed signs of respiratory irritation in animals at the three highest concentrations as indicated by increased respiratory frequency without an increase in pulmonary edema or lung weight                                [                             ADDIN                             EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>1992</Year><RecNum>14778</RecNum><DisplayText>[54]</DisplayText><record><rec-number>14778</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035219">14778</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alarie, Y.</author><author>Stock, M.F.</author></authors></contributors><titles><title>Respiratory Irritancy on a Mixture containing Polyethylene Glycol Mono(Octyl)Phenyl Eether CAS #9035-19-5</title><secondary-title>ChemView - U.S. Environmental Protection Agency</secondary-title></titles><periodical><full-title>ChemView - U.S. Environmental Protection Agency</full-title></periodical><pages>37, https://chemview.epa.gov/chemview/proxy?filename=09022526800b76c9_86960000465_09-26-2011_8D_PHCS_Original%20-

%2086960000465.pdf</pages><dates><year>1992</year></dates><urls></urls></record></Cite></EndNote>]. An acute inhalation exposure study in Syrian hamsters to 3.0 mg/L of octylphenoxypolyethoxyethanol to varying exposure durations reported that lung deposition of octylphenoxypolyethoxyethanol corresponded to mortality with an $LD_{50}$ of 1300-2100 µg [

ADDIN EN.CITE <EndNote><Cite><Author>Damon</Author><Year>1982</Year><RecNum>13323</RecNum><DisplayText>[55]</DisplayText><record><rec-number>13323</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1479320592">13323</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Damon, E. G.</author><author>Halliwell, W. H.</author><author>Henderson, T. R.</author><author>Mokler, B. V.</author><author>Jones, R. K.</author></authors></contributors><titles><title>Acute toxicity of polyethylene glycol p-isooctylphenol ether in syrian hamsters exposed by inhalation or bronchopulmonary lavage</title><secondary-title>Toxicology and applied pharmacology</secondary-title><alt-title>Toxicol Appl Pharmacol</alt-title></titles><periodical><full-title>Toxicology and Applied Pharmacology</full-title><abbr-1>Toxicol. Appl. Pharmacol.</abbr-1></periodical><pages>53-61</pages><volume>63</volume><number>1</number><edition>Damon, E G&#xD;Halliwell, W H&#xD;Henderson, T R&#xD;Mokler, B V&#xD;Jones, R K&#xD;1982/03/30</edition><keywords><keyword>Animals</keyword><keyword>Cricetinae</keyword><keyword>Detergents/ toxicity</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Female</keyword><keyword>Lethal Dose 50</keyword><keyword>Lung/ drug

effects/pathology</keyword><keyword>Male</keyword><keyword>Mesocricetus</keyword><

keyword>Octoxynol</keyword><keyword>Polyethylene Glycols/administration &amp; dosage/

toxicity</keyword><keyword>Surface-Active                                                                       Agents/

toxicity</keyword><keyword>Therapeutic

Irrigation</keyword></keywords><dates><year>1982</year><pub-dates><date>Mar

30</date></pub-dates></dates><isbn>0041-008X                                      (Print)&#xD;0041-008X

(Linking)</isbn><accession-num>7071873</accession-num><call-num>0  (Detergents)&#xD;0

(Surface-Active        Agents)&#xD;30IQX730WE        (Polyethylene        Glycols)&#xD;9002-93-1

(Octoxynol)</call-num><urls></urls><remote-database-provider>NLM</remote-database-

provider><language>Eng</language></record></Cite></EndNote>]. The authors concluded that

the deaths in these animals were likely the result of severe laryngeal edema and ulcerative

laryngitis while the lower airways and lungs in these animals were relatively free of serious

pathologies. The authors hypothesized that that these observed effects were due to large

tracheobronchial deposition following the aerosol exposure and the mucociliary clearance of the

deposited chemical resulted in a large concentration of the chemical on the laryngeal mucosa.

Finally, in the only repeated dose inhalation exposure identified for nonionic surfactants, a 2-week

repeated whole-body dose inhalation study was conducted on octylphenoxypolyethoxyethanol in

male and female Sprague-Dawley rats to 5.3 and 10.3 mg/m$^3$ (5/sex/dose; MMAD 1.8 μm, GSD

1.8μm) for 6 hours/day, 5 days/week [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. Slight

to minimal subacute inflammation of the alveolar walls and hyperplasia of the alveolar/bronchiolar

epithelium was reported, in addition to an increase in slight discoloration of the lungs, increased

lung weight, and mucoid nasal discharge; a LOAEC of 5.3 mg/m$^3$ was identified.

*Mechanistic studies*

*In vitro* studies of surfactant effects on cell membranes have provided evidence of possible MOAs. Warisnoicharoen *et al.* (2003) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ] evaluated the cytotoxicity of the nonionic surfactants polyoxyethylene-10-oleyl ether ($C_{18:1}E_{10}$), polyoxyethylene-10-dodecyl ether ($C_{12}E_{10}$), and N,N-dimethyl-dodecylamine-N-oxide ($C_{12}AO$; CASRN 1643-20-5) to cultured human bronchial epithelium cells (16-HBE14o-) *in vitro*, using the MTT cell viability assay. All of the surfactants tested were cytotoxic at concentrations near or below their critical aggregation (micellular) concentrations (as determined by surface tension measurements), suggesting that surfactant toxicity was due to the disruption caused by the partitioning of monomeric surfactant into the cell membrane.

Lindenberg *et al.* (2019) [ ADDIN EN.CITE <EndNote><Cite><Author>Lindenberg</Author><Year>2019</Year><RecNum>14779</RecNum><DisplayText>[57]</DisplayText><record><rec-number>14779</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035601">14779</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lindenberg, F.</author><author>Sichel, F.</author><author>Lechevrel, M.</author><author>Respaud, R.</author><author>Saint-Lorant, G.</author></authors></contributors><titles><title>Evaluation of Lung Cell Toxicity of Surfactants for Inhalation Route</title><secondary-title>Journal of Toxicology and risk assessment</secondary-title></titles><periodical><full-title>Journal of Toxicology and risk

assessment</full-title></periodical><pages>https://doi.org/10.23937/2572-4061.1510022</pages><volume>5</volume><number>1</number><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>] evaluated the cytotoxic activity of the three nonionic polymeric surfactants, which are commonly used in formulations of nebulized pharmaceuticals to prevent protein agglomeration, Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80) and Poloxamer 188 in a BEAS-2B human bronchial epithelial cell model by using an innovative air-liquid interface (ALI) method of exposure compared to the classical liquid/liquid (L/L) model. The study measured the release of Lactate Dehydrogenase (LDH) which is an intercellular enzyme present in large amounts in the cytoplasm. Loss of membrane integrity will cause the release of LDH into the extracellular medium. Cytotoxicity of Polysorbate 20 was observed at concentrations of 1-2% (v/v) when using the more biologically relevant ALI method by measuring Lactate Dehydrogenase (LDH) activity, however, a significant increase in LDH was only observed at 4% for Polysorbate 80 and not significantly increased at concentrations of up to 10% for Poloxamer 188. These results suggest that Polysorbate 20 and to the lesser extent Polysorbate 80 induce damage to the cell membrane integrity while the linear Poloxamer 188 did not demonstrate any *in vitro* cytotoxicity.

Altogether, the available *in vitro* and *in vivo* data indicate a wide discrepancy in respiratory toxicity among nonionic surfactants. The small dataset presented in this section preclude establishing correlations between respiratory effects and chemical properties such as surface tension or CMC. Others have examined the relationship between chemical properties of nonionic surfactants and eye irritation and concluded that hydrophilic-lipophilic balance, pH, alkyl chain length, or poly [oxyethylene] chain lengths failed to predict eye irritation potential across the nonionic

[PAGE  ]

subcategory [ ADDIN EN.CITE

<EndNote><Cite><Author>Heinze</Author><Year>1999</Year><RecNum>14780</RecNum><DisplayText>[58]</DisplayText><record><rec-number>14780</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035990">14780</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Heinze, J.E.</author><author>Casterton, P.L.</author><author>Atrash, J.</author></authors></contributors><titles><title>Relative Eye Irritation Potential of Nonionic Surfactants: Correlation to Dynamic Surface Tension</title><secondary-title>Journal of toxicology: cutaneous and ocular toxicology</secondary-title></titles><periodical><full-title>Journal of toxicology: cutaneous and ocular toxicology</full-title></periodical><pages>359-374, https://doi.org/10.3109/15569529909065552</pages><volume>18</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. However, significant correlations of eye irritation and the maximum reduction in surface tension were observed at the CMC or higher surfactant concentration when conducted under nonequilibrium conditions. Whether this chemical property similarly predicts potency of nonionic surfactants for respiratory effects requires additional data and analysis outside of the scope of this summary.

**Anionic Surfactants**

*In vivo studies*

Two acute inhalation toxicity studies were identified for anionic surfactants which demonstrated high toxicity via the inhalation route. Oleoyl sarcosine, which is irritating to the skin and damaging to the eye [ ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14781</RecNum ><DisplayText>[59]</DisplayText><record><rec-number>14781</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036160">14781</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>N-methyl-N-[C18-(unsaturated)alkanoyl]glycine, CASRN: NA, EC number: 701-177-3, Skin irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/21429/7/4/2/?documentUUID=fbaef057-ecc7-4763-aa56-1fa2c88c606c</pages><dates><year>2020</year></dates><urls></urls></record></Cite></End Note>], was evaluated in a 4-hour nose-only inhalation study in male and female Sprague-Dawley rats using concentrations of 0.3, 0.6, 2.2, and 3.7 mg/L (300, 600, 2,200, 3,700 mg/m$^3$). An LC$_{50}$ of 1.37 mg/L was identified with edema of the lung at 0.6 mg/L and audible gasping at 0.3 mg/L. For sodium lauroyl sarcosinate (CASRN 137-16-6), which is irritating to the eye but not the skin, male Wistar rats were exposed to a 4-hour nose-only inhalation concentration of 0.05, 0.5, 1, and 5 mg/L (50, 500, 1,000, and 5,000 mg/m$^3$) (MMAD 4.4, 2.85, 3.65, 6; GSD 2.7, 3, 4.2, 2.9, respectively and 5 female rats were exposed to 1.1 or 5.5 mg/L (MMAD 3.65, 6; GSD 4.2, 2.9, respectively)[ ADDIN EN.CITE

[PAGE ]

&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Dossier&lt;/Author&gt;&lt;Year&gt;2020&lt;/Year&gt;&lt;RecNum&gt;14782&lt;/RecNum&gt;&lt;DisplayText&gt;[60, 61]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;14782&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036284"&gt;14782&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Registration Dossier&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Sodium N-lauroylsarcosinate, CASRN: 137-16-6, EC number: 205-281-5, Eye Irritation&lt;/title&gt;&lt;secondary-title&gt;European Chemicals Agency&lt;/secondary-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;European Chemicals Agency&lt;/full-title&gt;&lt;/periodical&gt;&lt;pages&gt;https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/14123/7/4/3&lt;/pages&gt;&lt;dates&gt;&lt;year&gt;2020&lt;/year&gt;&lt;/dates&gt;&lt;urls&gt;&lt;/urls&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;Cite&gt;&lt;Author&gt;Dossier&lt;/Author&gt;&lt;Year&gt;2020&lt;/Year&gt;&lt;RecNum&gt;14783&lt;/RecNum&gt;&lt;record&gt;&lt;rec-number&gt;14783&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036540"&gt;14783&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Registration Dossier&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Sodium N-lauroylsarcosinate, CASRN: 137-16-6, EC number: 205-281-5, Acute Toxicity: Inhalation&lt;/title&gt;&lt;secondary-title&gt;European Chemicals Agency&lt;/secondary-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;European Chemicals Agency&lt;/full-title&gt;&lt;/periodical&gt;&lt;pages&gt;https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/14123/7/3/3&lt;/pages&gt;&lt;dates&gt;&lt;year&gt;2020&lt;/year&gt;&lt;/dates&gt;&lt;urls&gt;&lt;/urls&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. All 10 animals exposed to 5 mg/L died within 1-2 h of dosing, and 4/5 of the animals

exposed to 0.5 mg/L and the 10 animals exposed to 1 mg/ml died within 1-2 days after dosing. Animals in the 0.05 mg/L had no clinical signs or mortality at the conclusion of the study. At necropsy, red foci were noted on the lungs in animals of groups receiving concentrations of $\geq 0.5$ mg/L. The $LC_{50}$ was reported to be 0.05-0.5 mg/L. Carboxylic acid compounds, such as oleoyl sarcosine, have a carboxyl group pKa value of ~5, thus at physiological pH values maintained near 7 in the lung, the carboxyl group will be 99% in the anionic form according the Henderson-Hasselbalch equation. Since sodium is the major cation in mammalian body fluids (~145 mM), the use of the sodium oleoyl sarcosine data is appropriate for POD derivation.

Repeated-dose inhalation studies were identified for oleoyl sarcosine (CASRN 110-25-8), and dioctyl sodium sulfosuccinate (CASRN 577-11-7). Oleoyl sarcosine was evaluated in a 28-day nose-only inhalation study (6 hours/day, 5 days/week; OECD Guideline 412) in male and female Fischer rats (5/group/sex) using concentrations of 0, 0.006, 0.02, or 0.06 mg/L (6, 20, 60 mg/m$^3$) (MMAD 1.11, 1.15, 1.22μm, GSD 1.68-2.57μm) in 10% ethanol for 6 hours/day, 5 days/week in 10% ethanol [ ADDIN EN.CITE

<EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14784</RecNum><DisplayText>[62]</DisplayText><record><rec-number>14784</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596036869">14784</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>N-methyl-N-[C18-(unsaturated)alkanoyl]glycine, CASRN: NA, EC number: 701-177-3, Repeated dose toxicity: Inhalation</title><secondary-title>European Chemicals Agency</secondary-

title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/21429/7/6/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. The mass median aerodynamic diameter (MMAD) of the aerosol particles were 1.11- 1.22 μm and the geometric standard deviation (GSD) was 1.68-2.57. Changes in the mean corpuscular volume (MCV), white blood cells (WBC), and lymphocytes in male animals of the high dose groups were observed. In female animals of the mid-dose group, reticulocyte counts were significantly reduced. Reflex bradypnea was noted in the animals of the mid and high doses which is associated with severely irritating substances. All test concentrations caused effects at several sites of the respiratory tract with indications for local irritation, such as squamous metaplasia and epithelium proliferation and submucous acute inflammation at the base of the epiglottis. In the lungs and bronchi, the most prominent finding was a focal early stage of fibrosis, but details were not provided at the dose level for this effect. Lung weights were increased at the highest dose. The LOAEC was 0.006 mg/L (6 mg/m$^3$) air in males and females; the basis for the effect level was local irritation.

Dioctyl sodium sulfosuccinate (DOSS) was evaluated in a 13-week inhalation study in male and female Sprague-Dawley rats (12/group/sex), to an aerosol of a product containing 0.0042 mg/L (4.2 mg/m$^3$) DOSS, for 4 hours a day, 5 days a week [ ADDIN EN.CITE <EndNote><Cite><Author>CIR</Author><Year>2013</Year><RecNum>14785</RecNum><DisplayText>[63]</DisplayText><record><rec-number>14785</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596037107">14785</key></foreign-keys><ref-type name="Journal

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Panel Meeting, June 10-11, 2013</title><secondary-title>Cosmetic Ingredient Review (CIR),
Washington, D.C.</secondary-title></titles><periodical><full-title>Cosmetic Ingredient Review
(CIR), Washington, D.C.</full-title></periodical><pages>171, https://www.cir-
safety.org/sites/default/files/Sulfosuccinates_RR.pdf</pages><dates><year>2013</year></dates
><urls></urls></record></Cite></EndNote>]. There were no statistically significant differences
in dosed and control groups, for the mean body weight gain, survival, appearance and behavior,
urinalysis values, and microscopic lesions. Significant differences were noted in the blood such as
elevated erythrocytic values in male rats at 7 weeks and depressed mean corpuscular hemoglobin
concentration values in male rats at 13 weeks. At 7 weeks, the lungs of animals necropsied were
stained with Oil Red O and examined; scattered foci of neutrophils and an increase in alveolar
macrophages were reported in a single dosed male rat. A LOAEC of 4.2 mg/m$^3$ was identified
based on blood effects in male rats.


*Mechanistic studies*

Mechanistic studies examining the pulmonary effects of anionic surfactants have been studied in
dogs and/or sheep exposed, dioctyl sulfosuccinate sodium salt. (DOSS; CASRN 577-11-7).
Increased minimum surface tension of lung extract or bronchioalveolar lavage fluid (BALF) was
observed in dogs and sheep following *in vivo* aerosol exposure to the anionic detergent dioctyl
sodium sulfosuccinate (DOSS) in 1:1 mixture of ethanol and saline for 30 – 60 minutes, at a
concentration that was selected to ensure a moderate degree of edema (estimated dose of 15 mg

detergent/kg body weight) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA   ]. Light microscopic examination of the lungs 4 hours after exposure to DOSS aerosol observed no grossly destructive effects on alveolar cells or lung architecture in exposed dogs. However, a decrease in pulmonary compliance was observed that the authors hypothesized was due to an increase in surface tension in the alveoli in the presence of detergent.

Pulmonary clearance studies using radiolabeled aerosol tracers have evaluated whether detergent effects on the surfactant layer lead to increased alveolar permeability.  For example, inhalation exposure to DOSS enhanced the pulmonary clearance of radiolabeled diethylenetriamine pentaacetic acid (DTPA), a relatively small hydrophilic molecule, reflecting increased alveolar permeability after detergent exposure [ ADDIN EN.CITE    ADDIN EN.CITE.DATA   ]. In most studies, this effect on alveolar permeability was seen in the absence of effects on blood gas levels or pulmonary compliance that occur with higher exposure, indicating that the increase in alveolar permeability is a sensitive effect of detergent aerosol. The effect was demonstrated to be concentration-related in one study in which multiple dilutions of the liquid detergent were nebulized [ ADDIN EN.CITE    ADDIN EN.CITE.DATA   ]. Some studies also evaluated the clearance of a radiolabeled aerosol of albumin, a much larger molecule, which was enhanced by DOSS as well, but to a lesser degree than DTPA [ ADDIN EN.CITE    ADDIN EN.CITE.DATA   ]. Wang *et al*. (1993) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA   ] observed an increase in protein flux from plasma to alveolar space after DOSS inhalation in sheep, which the authors attributed to disruption of the alveolar lining and increased microvascular permeability. The increased alveolar permeability observed in these studies has been hypothesized to result from increased alveolar surface tension, which could cause increased permeability either by opening

[PAGE  ]

previously closed pores (through which solutes pass) in the membrane or by stretching already open pores [ ADDIN EN.CITE      ADDIN EN.CITE.DATA    ]. However, as previously mentioned, surfactants can disrupt cell membranes; thus, this mechanism may be an alternate explanation                           [                    ADDIN                    EN.CITE

<EndNote><Cite><Author>Burden</Author><Year>2012</Year><RecNum>14727</RecNum
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D.W.</author></authors></contributors><titles><title>Guide to the Disruption of Biological
Samples  -  2012,  Version  1.1.</title><secondary-title>Random  Primers</secondary-title></titles><periodical><full-title>Random          Primers</full-title></periodical><pages>1-25</pages><number>12</number><dates><year>2012</year></dates><urls></urls></record>
</Cite></EndNote>].

## Cationic Surfactants

### *In vivo studies*

Three acute inhalation toxicity studies were identified for DDAC, Dioctadecyldimethylammonium chloride (DODMAC), and BAC. DDAC, which is corrosive to the skin and severely damaging to the                    eye                    [                    ADDIN                    EN.CITE

<EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14786</RecNum
><DisplayText>[71]</DisplayText><record><rec-number>14786</rec-number><foreign-keys><key              app="EN"              db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596038295">14786</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Skin irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/5864/7/4/2</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], was tested in rats (5/sex/dose, unspecified strain) exposed via inhalation to 0.05, 0.09, 0.13, 0.25, 1.36 mg/L, or 4.54 mg/L (50, 90, 130, 250, 1,360, 4,540 mg/m$^3$) for 2 hours and observed for 14 days. An LC$_{50}$ of 0.07 mg/L was identified based on unspecified abnormalities identified in several organs including the lungs [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><DisplayText>[10]</DisplayText><record><rec-number>14732</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018482">14732</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Subchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-

0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]

. A similar quaternary amine, DODMAC, which is irritating to the skin and causes serious damage to the eyes, was tested in Albino rats (10 males, strain not specified) to the test substance (1:29 distilled water) *via* inhalation at 180 mg/L (180,000 mg/m$^3$) for one hour and observed for 14 days

[ ADDIN EN.CITE <EndNote><Cite><Author>EURAR</Author><Year>2009</Year><RecNum>14787</RecNum><DisplayText>[72]</DisplayText><record><rec-number>14787</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596038841">14787</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EURAR</author></authors></contributors><titles><title>European Union Risk Assessment Report (EURAR), CAS No: 107-64-2, EINECS No: 203-508-2, dimethyldioctadecylammonium chloride (DODMAC)</title><secondary-title>European Commission, Joint Research Centre, Institute for Health and Consumer Protection (IHCP), former Toxicology and Chemical Substances (TCS) European Chemicals Bureau (ECB)</secondary-title></titles><periodical><full-title>European Commission, Joint Research Centre, Institute for Health and Consumer Protection (IHCP), former Toxicology and Chemical Substances (TCS) European Chemicals Bureau (ECB)</full-title></periodical><pages>123, https://echa.europa.eu/documents/10162/46f2f114-12ff-4af4-8da7-72148b6a202e</pages><volume>14</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. No mortalities were reported and observed treatment-related clinical signs included preening, excessive masticatory (chewing) movements, excessive salivation stains, lacrimation, serosanguineous stains around the nose and labored respiration. All

animals appeared normal one day after dosing. The $LD_{50}$ (1h) was > 180 mg/L. BAC, which is corrosive to the skin and causes severe eye damage [ ADDIN EN.CITE      ADDIN EN.CITE.DATA    ], was tested in female Wistar rats (5/group) exposed via nose-only inhalation to 37.6 and 53 mg/m$^3$ for 4 hours and observed for 14 days or exposed to 30.6 mg/m$^3$ for 6 hours and BALF was measured 18 hours post-exposure [ ADDIN EN.CITE <EndNote><Cite><Author>Swiercz</Author><Year>2008</Year><RecNum>14789</RecNum ><DisplayText>[74]</DisplayText><record><rec-number>14789</rec-number><foreign-keys><key          app="EN"          db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596039305">14789</key></foreign-keys><ref-type          name="Journal Article">17</ref-type><contributors><authors><author>Swiercz, R.</author><author>Hałatek, T.</author><author>Wasowicz,   W.</author><author>Kur,   B.</author><author>Grzelińska, Z.</author><author>Majcherek,          W.</author></authors></contributors><auth-address>Department of Toxicology and Carcinogenesis, Nofer Institute of Occupational Medicine, Łódź, Poland. radek@imp.lodz.pl</auth-address><titles><title>Pulmonary irritation after inhalation exposure to benzalkonium chloride in rats</title><secondary-title>Int J Occup Med Environ Health</secondary-title><alt-title>International journal of occupational medicine and environmental health</alt-title></titles><periodical><full-title>International journal of occupational medicine and environmental health</full-title><abbr-1>Int J Occup Med Environ Health</abbr-1></periodical><alt-periodical><full-title>International journal of occupational medicine and environmental health</full-title><abbr-1>Int J Occup Med Environ Health</abbr-1></alt-periodical><pages>157-63</pages><volume>21</volume><number>2</number><edition>2008/08/22</edition><keyw ords><keyword>Animals</keyword><keyword>Benzalkonium          Compounds/administration

&amp; dosage/*toxicity</keyword><keyword>Female</keyword><keyword>Inhalation Exposure</keyword><keyword>Lung Diseases/*chemically induced/pathology</keyword><keyword>Organ Size/drug effects</keyword><keyword>Rats</keyword><keyword>Rats, Wistar</keyword></keywords><dates><year>2008</year></dates><isbn>1232-1087 (Print)&#xD;1232-1087</isbn><accession-num>18715840</accession-num><urls></urls><electronic-resource-num>10.2478/v10001-008-0020-1</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The identified $LC_{50}$ was approximately 53 mg/m$^3$ and BALF analysis reported increased inflammatory markers such as TNF-a, IL-6 and an increase in indicators of lung damage such as LDH, total protein, and increased lung weight.

Three repeated dose inhalation studies of three different exposure durations were identified for DDAC: 14-day, 28-day, and 90-day.

In the 14-day study, male Sprague-Dawley rats were exposed via whole-body inhalation exposures to DDAC aerosols of 0.15 mg/m$^3$, 0.6 mg/m$^3$, and 3.6 mg/m$^3$ (MMAD 1.86μm, GSD 2.75 μm) for 6 hours/day, 7 days/week [ ADDIN EN.CITE <EndNote><Cite><Author>Lim</Author><Year>2014</Year><RecNum>14790</RecNum><DisplayText>[75]</DisplayText><record><rec-number>14790</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596039544">14790</key></foreign-keys><ref-type name="Journal

[PAGE  ]

ED_005294A_00000384-00084

Article">17</ref-type><contributors><authors><author>Lim, C. H.</author><author>Chung, Y. H.</author></authors></contributors><auth-address>Toxicity Research Team, Occupational Safety and Health Research Institute, KOSHA, Daejeon, Korea.</auth-address><titles><title>Effects of didecyldimethylammonium chloride on sprague-dawley rats after two weeks of inhalation exposure</title><secondary-title>Toxicol Res</secondary-title><alt-title>Toxicological research</alt-title></titles><periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></periodical><alt-periodical><full-title>Toxicol Res</full-title><abbr-1>Toxicological research</abbr-1></alt-periodical><pages>205-10</pages><volume>30</volume><number>3</number><edition>2014/10/25</edition><keywords><keyword>Biocide</keyword><keyword>Didecyldimethylammonium chloride</keyword><keyword>Inhalation</keyword></keywords><dates><year>2014</year><pub-dates><date>Sep</date></pub-dates></dates><isbn>1976-8257 (Print)&#xD;1976-8257</isbn><accession-num>25343015</accession-num><urls></urls><custom2>PMC4206748</custom2><electronic-resource-num>10.5487/tr.2014.30.3.205</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Mild effects were noted in the bronchoalveolar cell differentiation counts, cell damage parameters in the BAL fluids, in addition to inflammatory cell infiltration, and interstitial pneumonia of the medium and high groups. The NOAEC was determined to be 0.15 mg/m$^3$.

In the intermediate exposure (4-week) study, male and female Sprague-Dawley rats (5

rats/sex/group) were exposed via dynamic nose-only inhalation for 6 hours/day, 5 days/week to

concentrations of 0, 0.08, 0.5, and 1.5 mg/m$^3$ DDAC (MMAD 1.4-1.9 μm, GSD 1.83-1.86 μm)

for 6 hours/day, 5 days/week [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><

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D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and

Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-

title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-

0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]

. Lung weights were increased in females in the mid- and high-concentration groups and in males

in the high concentration group. The bronchoalveolar lavage fluid (BALF) analysis indicated that

at the high concentration neutrophils and eosinophils increased with a concomitant decrease in

macrophages. Ulceration of the nasal cavity was observed in males and females in the high

concentration group. In males, there was an increase in cell count and total protein across all

doses. In females, there was an increase in LDH across all concentrations, but the small sample

size precluded establishing statistical significance for the effects. Minimal to mild increased

mucus of the respiratory epithelium was observed in males and females at all concentrations. A conservative LOAEC of 0.08 mg/m$^3$ was identified based on increased mucus of the respiratory epithelium and increased LDH; however, due to the mild effects and low number of animals/group, the effects were not statistically significant.

In the 13-week sub-chronic study, male and female Sprague-Dawley rats (10/group/sex) were exposed in whole body exposure chambers to concentrations of 0.11, 0.36, and 1.41 mg/m$^3$ DDAC (MMAD 0.63-1.65 μm, GSD 1.62-1.65 μm) for 6 hours/day, 5 days/week [ ADDIN EN.CITE

&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Kim&lt;/Author&gt;&lt;Year&gt;2017&lt;/Year&gt;&lt;RecNum&gt;14736&lt;/RecNum&gt;&lt;DisplayText&gt;[76]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;14736&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018905"&gt;14736&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Kim, Y. S.&lt;/author&gt;&lt;author&gt;Lee, S. B.&lt;/author&gt;&lt;author&gt;Lim, C. H.&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;auth-address&gt;Chronic Inhalation Toxicity Research Center, Chemicals Toxicity Research Bureau, Occupational Safety and Health Research Institute, KOSHA, Daejeon, Korea.&lt;/auth-address&gt;&lt;titles&gt;&lt;title&gt;Effects of Didecyldimethylammonium Chloride (DDAC) on Sprague-Dawley Rats after 13 Weeks of Inhalation Exposure&lt;/title&gt;&lt;secondary-title&gt;Toxicol Res&lt;/secondary-title&gt;&lt;alt-title&gt;Toxicological research&lt;/alt-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Toxicol Res&lt;/full-title&gt;&lt;abbr-1&gt;Toxicological research&lt;/abbr-1&gt;&lt;/periodical&gt;&lt;alt-periodical&gt;&lt;full-title&gt;Toxicol Res&lt;/full-title&gt;&lt;abbr-1&gt;Toxicological research&lt;/abbr-1&gt;&lt;/alt-periodical&gt;&lt;pages&gt;7-14&lt;/pages&gt;&lt;volume&gt;33&lt;/volume&gt;&lt;number&gt;1&lt;/number&gt;&lt;edition&gt;2017/01/31&lt;/edition&gt;&lt;keyw

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BAC was evaluated in a 2-week whole-body inhalation study in male and female Fischer rats (5/group/sex) to concentrations of 0.8, 4 and 20 mg/m$^3$ (MAMD 1.09-1.61 µm, GSD 1.51 to 2.00 µm) for 6 hours/day, 7 days/week [ ADDIN EN.CITE     ADDIN EN.CITE.DATA     ].

Exposure-related effects were observed in the upper airway. Nasal discharge, rale, and deep respiration were observed in the high concentration, and nasal discharge was observed in the low and mid concentrations. In the nasal cavity, ulceration with suppurative inflammation, squamous metaplasia, and erosion with necrosis were observed in the respiratory epithelium and transitional epithelium of the male and female high concentrations.

Degeneration and regeneration of terminal bronchiolar epithelium, smooth muscle hypertrophy of bronchioloalveolar junction, and cell debris in the alveolar lumens were observed in the mid and high concentration male groups and high concentration dose female group. Hypertrophy and hyperplasia of mucous cells in the bronchi or bronchiole were observed in both males and females. The authors hypothesized that BAC has greater deposition to the upper respiratory tract due to mucociliary clearance and emergency airway response caused by the irritating effects of BAC. The squamous metaplasia of the respiratory epithelium and transitional epithelium, mucinous cell hypertrophy and proliferation of the respiratory epithelium, mucinous cell metaplasia of the transitional epithelium in the nasal cavities, and mucinous cell hypertrophy and proliferation of terminal bronchiole were considered adaptive changes after tissue injury. In the BALF analysis, the concentration of ROS/RNS, IL-1$\beta$, IL-6, and MIP-2 decreased dose dependently at the end of the exposure period but did not show a concentration-dependent change at 4 weeks of recovery. In addition, the concentrations of TNF-$\alpha$, IL-4, and TGF-$\beta$ did not show changes associated with test substance exposure. Finally, relative lung weights were statistically significantly increased in males at the mid and high doses and in females at the high doses only. The study authors identified a LOAEC of 0.8 mg/ $m^3$ based on effects in the nasal cavity.

[PAGE ]

*Mechanistic studies*

In vitro assays have demonstrated that cytotoxic effects of cationic surfactants have significantly greater toxicity to non-polarized than polarized mammalian cells [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. In this study, cell viability as measured by LDH and MTT assays in non-polarized HeLa and dendritic FSDC was more sensitive to the effects of different cationic surfactants of varying alkyl chain length and polar head groups than polarized cell lines MDCK and Caco-2. The authors concluded that cationic surfactant toxicity occurs well below their CMC, with greater toxicity associated with alkyl lengths of 10-12 than 14-16, however this association was not strictly linearly dependent. In addition, the cationic surfactants with a larger polar head group (i.e., benzalkonium) were 2-5 times more toxic than cationic surfactants with a more localized charge (i.e., trimethylammonium).

The effects of BAC on cell viability, inflammatory response and oxidative stress of human alveolar epithelial cells has been replicated in vitro using a dynamic culture condition to reflect the natural microenvironment of the lung [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. Normal breathing levels were simulated (tidal volume 10%, 0.2Hz) through surface elongation of an elastic membrane in a dynamic culture system. This type of dynamic system provided easy control of breathing rate during lung cell culture. The system assessed toxicity using different BAC concentrations (0, 2, 5, 10, 20, and 40 µg/mL) under static and dynamic culture conditions. Following 24 hr exposure to BAC, cellular metabolic activity, interleukin-8 (IL-8) and reactive oxygen species (ROS) levels demonstrated significant differences when using either static or dynamic cell growth conditions. The dynamic culture system, which more closely mimics lung conditions, showed a higher toxic response to BAC as indicated by increased ROS levels.

[PAGE ]

**Dose-Response Analysis: Quantitative Points of Departure (PODs)**

The limited animal inhalation toxicity data identified by the literature search and PODs from the studies are summarized in [ REF _Ref46931035 \h \* MERGEFORMAT ]. All of the identified data are from animal studies and therefore need to be extrapolated to estimate the human inhalation exposure (EPA, 1994) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum>< DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Previously, the exposure duration adjustment was described. EPA has also developed guidance focused on improving the science underlying the animal-to-human uncertainty factor and provides generalized procedures for deriving dosimetric adjustment factors (DAF) [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 22]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research</full-title>

Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Application of DAFs to the animal airborne exposure values yields estimates of the concentration that would result in the same concentration to humans, that is, the Human Equivalent Concentration (HEC). Application of a DAF in the calculation of a HEC is considered to address the toxicokinetic aspects of the animal-to-human UF (*i.e.*, to estimate from animal exposure information the human exposure scenario that would result in the same dose to a given target tissue) (EPA, 2002). This procedure involves the use of species-specific physiologic and anatomic factors relevant to the form of pollutant (*e.g.*, particle or gas) and categorized with regard to elicitation of response. These factors are all employed in determining the appropriate DAF. For HECs, DAFs are applied to the "duration-adjusted" concentration to which the animals were exposed (*e.g.*, to a weekly average). The generalized DAF procedures may also employ chemical-specific parameters, such as mass transport coefficients, when available.

The Regional Deposited Dose Ratio (RDDR) was used to derive DAFs for each of the surfactants with available animal toxicity studies. The RDDR is the ratio of the deposited dose in a respiratory tract region (r) for the laboratory animal species of interest ($RDD_A$) to that of humans ($RDD_H$) and was derived according to EPA's "*Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*" (EPA, 1994) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

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Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

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Protection Agency, Research Triangle Park, NC</secondary-title></titles><periodical><full-

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Triangle Park, NC</full-title></periodical><pages>389,

https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>]. EPA's RDDR software allows calculation of calculate RDDRs in various regions of the

respiratory tract for animals versus humans (*i.e.*, extra-thoracic, tracheobronchial, pulmonary,

thoracic, total respiratory tract and extra-respiratory regions). The RDDR calculation is based on

the characteristics of the aerosol tested in the inhalation study (Median Mass Aerodynamic

Diameter or MMAD, Geometric Standard Deviation or GSD), animal species, animal mass,

gender, etc. The RDDR selected as the DAF is informed by the effects (clinical signs, tissue

effects, biochemical changes) observed in the animal toxicity study and the aerosol

characteristics in the inhalation study. The summary of RDDR inputs (*e.g.*, MMAD and GSD)

and results are provided in [ REF _Ref46931035 \h \* MERGEFORMAT ] for each of the

toxicity studies from which PODs could be identified.

For the nonionic surfactant, octylphenoxypolyethoxyethanol, the effects observed (increased lung weights, alveolar/bronchiolar epithelial hyperplasia and lung inflammation) are consistent with lung effects in the LRT such that the pulmonary region RDDR (0.564) was used to calculate the HEC. For the anionic surfactant, oleoylsarcosine, the effects were seen in multiple regions of the respiratory tract, including squamous metaplasia and epithelium proliferation and submucous acute inflammation at the base of the epiglottis and early stages of fibrosis in the alveoli walls. Therefore, total respiratory tract RDDR (1.504 for males and 0.970 for females) was used to calculate the HEC. In both 21- and 90-day inhalation studies with DDAC, effects observed (changes in BALF LDH, BALF total protein, BALF cell count (males only), increase in mucus in the respiratory epithelium, and increase in mucoid exudate, inflammatory cell infiltration and interstitial pneumonia) were indicative that the pulmonary RDDR (0.42 for 14 and 90-day exposures and 0.5 to 0.6 for 28-day exposure) is appropriate for calculating the HEC. In contrast, for the cationic surfactant, benzalkonium chloride histopathological cellular changes were observed in the nasal cavity and lungs, indicating the total respiratory tract RDDR should be used to calculate the HEC. The RDDRs applied and HECs derived from the animal study PODs are provided in [ REF _Ref46931035 \h \* MERGEFORMAT ].

Commented [HT26]: SALAZAR:
I think total respiratory tract RDDR needs to be modeled not just the pulmonary region. Damon et al. demonstrated that effects occured in the laryngeal region. In addition you have effects in the TB region indicated by bronhiolar hyperplasia, and nasal effects as well.

Commented [HT27R26]: Annie – what do you think...RDDR for Total or PU or both??

Commented [HT28]: SALAZAR:
In the 21-day study, there is an increase in mucus of the respiratory epithelium , olfactory epithelium, and larynx. The total respiratory tract RDDR needs to be calculated here as well.

Commented [HT29R28]: Annie – what do you think? Total or PU?

[PAGE  ]

**Table [ SEQ Table \* ARABIC ].** Inhalation Toxicity Points of Departure and Human Equivalent Concentrations (HEC) for Surfactants.

| Surfactant Type | Category Analogue(s) | Inhalation Exposure Duration/Type | Study POD | Value | Reference | RDDR Model Input Parameters | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | MMAD ($\mu$m) | GSD ($\mu$m) | RDDR[+] | HEC mg/m$^3$ |
| Nonionic | octylphenoxy polyethoxyeth anol (CASRN 9002-93-1) | 14-day, 6 hr/d, 5 d/wk; whole body dosing | LOAEC | 5.3 mg/m$^3$ | [ HYPERL INK "http://w ww.deq.st ate.mi.us/ aps/downl oads/ATS L/9002-93-1/9002-93-1_annual_ ITSL.pdf" ] | 1.80 | 1.80 | $RDDR_{PuMale} = 0.564$ $RDDR_{PuFemale} = 0.610$ | male 2.989 female 3.323 |
| Anionic | oleoyl sarcosine (CASRN 110-25-8), | 28-day, 6 hr/d, 5 d/wk; nose-only (OECD 412) | LOAEC | 6 mg/m$^3$ (0.006 mg/L) | [ HYPERL INK "https://ec ha.europa. eu/hr/regi stration-dossier/-/registere d-dossier/21 | 1.16 | 2.12 | $RDDR_{TotMale} = 1.504$ $RDDR_{TotFemale} = 0.970$ | male < 9 .024 female < 5.820 |

[PAGE  ]

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 429/7/6/3"] | | | | |
| | dioctyl sodium sulfosuccinate (CASRN 577-11-7) | 13-week, 4 hr/d, 5 d/wk; | LOAEC (blood effects) | 4.2 mg/m³ | Cosmetic, Toiletry, and Fragrance Associati on (CTFA). 1991. Submissio n of unpublish ed data. | NA | NA | NA | NA |
| Cationic | DDAC | 14-day, 6 hr/d, 7 d/wk; whole body | NOAEC | 0.15 mg/m³ | Lim et al, 2014 | 1.86 | 2.75 | RDDR$_{PuMale}$ = 0.427 Only males tested | male 0.064 |
| | DDAC | 4-week, , 6 hr/d, 5 d/wk; nose-only | LOAEC * (lung effects) | 0.08 mg/m³ | EPA 2011 HQ-OPP-2006-0338-0045 | 1.60 | 1.85 | RDDR$_{Pu/Male}$ = 0.539  RDDR$_{PuFemale}$ = 0.583 | male 0.043  female 0.047 |
| | DDAC | 90-day, 6 hr/d, 5 d/wk; whole-body | NOAEC | 0.11 mg/m³ | Kim et al, 2017 | 0.86 | 1.63 | RDDR$_{PuMale}$ = 0.421 | male 0.046 male |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $RDDR_{PuFemale} = 0.420$ | female 0.046 |
| | BAC | 14-day, 6 hr/d, 7 d/wk; whole-body | LOAEC (nasal effects) | 0.8 mg/m³ | Choi et al., 2020 | 1.31 | 1.79 | $RDDR_{TotMale} = 1.414$<br><br>$RDDR_{TotFemale} = 0.991$ | male 1.131<br><br>female 0.793 |

*conservative estimate: effects were not statistically significant
+ RDDR values were calculated by RDDR.exe separately for male and female rats due to the differing body weights between genders
NA: Data not available or RDDR values could not be calculated from the available information
MMAD: Median Mass Aerodynamic Diameter of inhalation study aerosol
GSD: Geometric Standard Deviation of the inhalation study aerosol

*Benchmark Margin of Exposure Analysis*

The analogues shown in [ REF _Ref46931035 \h \* MERGEFORMAT ] provide representative examples of the types of PODs that may be applied to new chemistries that meet the Surfactant Criteria. Though the initial starting point for deriving a benchmark MOE is based on a composite of the default values of 10 for each of the individual values for $UF_H$, $UF_A$, and $UF_L$, refinements may be warranted based on dosimetric adjustments to the applied concentrations used for establishing the experimental PODs. As shown in [ REF _Ref46931035 \h \* MERGEFORMAT ], the data-derived uncertainty factors, RDDRs were used as DAFs to account for animal-to-human toxicokinetic difference.

In the case of surface-active substances like chemical substances meeting the Surfactant Criteria, EPA has recently adopted a generalized approach that has historically been applied on a case-by-case basis for chemical substances, in recognition that surface-active effects that lead to irritation/corrosion do not require absorption, metabolism, distribution, or elimination (ADME) (See, *e.g.*, EPA, 2020 [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>14794</RecNum>< DisplayText>[80]</DisplayText><record><rec-number>14794</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596040494">14794</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>H azard Characterization of Isothiazolinones in Support of FIFRA Registration

Review</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>84, https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2013-0605-0051&amp;contentType=pdf</pages><volume>EPA-HQ-OPP-2013-0605-0051</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

). In the context of this publication, irritation/corrosion include those effects in the respiratory tract that lead, for example, to inflammation, hyperplasia, and metaplasia. For chemical substances that act *via* a surface-active adverse outcome pathway (AOP), the default values for $UF_H$ and $UF_A$ are reduced to 3 (*i.e.*, $10^{0.5}$ or 3.162) to account for the uncertainty/variability for toxicodynamics, whereas the toxicokinetic component is reduced to 1 because ADME differences that would otherwise influence toxicokinetic differences are generally not relevant for surface-active substances. In order to apply these reductions, the following criteria must be established:

1. A description of the AOP,

2. A discussion of why the AOP is unlikely or likely to differ between humans, in the case of $UF_H$, or between animals, in the case of $UF_A$, and

3. A discussion as to why the ADME of the chemical substance is unlikely to play a role in the observed toxicity.

When the above criteria are met, application of the appropriate dosimetric adjustment factor (*i.e.*, RDDR) should still be applied, given that deposition is the most appropriate dosimetric for

assessing acute/subacute effects from surface-active agents. However, since the dosimetric adjustment factor accounts for toxicokinetic component of $UF_A$, no additional reductions should be incorporated.

Commented [HT32]: I changed this

Commented [ST33R32]: Language still needs to be cleared up based on today's call

Based on these information and criteria, the following composite values are appropriate to describe intra- and interspecies uncertainty/variability (*i.e.*, $UF_H \times UF_A$):

$UF_H$ = 10 or 3: The default value of 10 should be applied when the available information does not support each of the above criteria. If the available information supports all of the above criteria, then a value of 3 may be applied.

$UF_A$ = 10 or 3: The default value of 10 should be applied when the available information does not support the application of a dosimetric adjustment factor to quantifying a human equivalence concentration (HEC) or when the available information does not support each of the above criteria. If the available information allows derivation of an HEC and/or application of the above criteria, then a value of 3 may be applied.

$UF_L$ = 10 or 1: If the POD from the experimental study is based on a LOAEC, then a default value of 10 should be applied, unless there is information to support that a reduced value is warranted. If the experimental data are amenable to benchmark dose modeling, a BMCL should be calculated and a value of 1 should be applied for this area of uncertainty.

[PAGE ]

Taken together, the above considerations and approaches support application of a benchmark MOE ranging from 10 to 1,000 and will depend on the analogue used and available data on the new chemical substance. In those instances where the data are too limited to determine when an analogue is appropriate for extrapolating the hazards to the new chemical substance, experimental testing should be performed to aid with informing the quantitative assessment, as discussed under the Tiered-Testing Strategy.

*Uncertainties and Limitations*

The assessment framework outlined herein includes a number of uncertainties and limitations, include those associated with extrapolating the hazards identified from the analogues shown in shown in [ REF _Ref46931035 \h \* MERGEFORMAT ]. Uncertainties associated with using animal studies to estimate human toxicity are recognized and methods developed to reduce them

[ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2014</Year><RecNum>14795</RecNum> <DisplayText>[81]</DisplayText><record><rec-number>14795</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596040729">14795</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title >Guidance on Grouping of Chemicals, Second Edition, Series on Testing &amp; Assessment</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-title></titles><periodical><full-

title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</full-title></periodical><pages>141,

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&amp;doclanguage=en</pages><volume>ENV/JN/MONO(2014)4</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Exposure duration adjustment procedures for inhalation exposures and application of DAFs to derive HECs, are well-established procedures for reducing uncertainties associated with the toxicokinetic aspects of animal-to-human extrapolation factors and derivation of benchmark MOEs (*i.e.*, type and magnitude of uncertainty factors) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 22]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><

Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. Likewise, EPA has recommended that BMD modeling be employed whenever possible to identify a POD and to reduce uncertainties associated with using a LOAEL from a toxicity study.

Given the small number of chemical substances that meet the Surfactant Criteria that have concentration-response inhalation toxicity data, the applicability of these analogues to new chemical substances needs to be carefully considered, particularly given the influence of additional functional groups that may increase/decrease the toxicity of the new chemical substance compared to the analogue. Risk assessors should first consider the surface tension and CMC criteria provided in Table X, and compare them to these measurements for the new chemical substance, if available, or the influence additional functional groups present or absent from the new chemical would have

on these criteria (*e.g.*, would a particular functional group increase or decrease toxicity, for example by another mechanism of action). If such structural differences are judged not to significantly influence properties and toxicity, such that the new chemical substance is expected to have comparable or lower toxicity, read-across is an appropriate approach for characterizing hazards and risk. Of course, uncertainties regarding read-across should be acknowledged in the risk characterization.

For instances where the notifier of the new chemical substance and/or EPA is unable to conclude that one of the analogues in [ REF _Ref46931035 \h \* MERGEFORMAT ] is comparable to or represents a worse-case analogue compared to the new chemical substance, then the Tiered-Testing Strategy provided herein could be used to inform whether the new chemical substance has lower, comparable, or higher toxicity to the representative analogue in the respective subcategory. Prior to conducting such testing, the scientific basis for selecting an analogue as the comparator compound to the new chemical substance should be understood and a rationale provided as to why the analogue is anticipated to have comparable or higher toxicity than the new chemical substance.

**Use of New Approach Methods (NAMs) and *In Vitro* Testing Strategies to Reduce or Replace Vertebrate Testing**

The amended TSCA requires EPA to reduce reliance on animal testing using methods and strategies that "provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment" [ ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>14796</RecNum> <DisplayText>[82]</DisplayText><record><rec-number>14796</rec-number><foreign-

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Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of

Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-

title></titles><periodical><full-title>United States Code (U.S.C.)</full-

title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53

&amp;edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cit

e></EndNote>]. Additionally, in 2019, EPA was directed to prioritize efforts to use NAMs to

reduce animal testing [ ADDIN EN.CITE

<EndNote><Cite><Author>Wheeler</Author><Year>2019</Year><RecNum>14797</RecNu

m><DisplayText>[83]</DisplayText><record><rec-number>14797</rec-number><foreign-

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A.R.</author></authors></contributors><titles><title>Directive to Prioritize Effects to Reduce

Animal Testing</title><secondary-title>United States Environmental Protection

Agency</secondary-title></titles><periodical><full-title>United States Environmental

Protection Agency</full-title></periodical><pages>3,

https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-

231249.pdf</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndN

ote>]. Multiple NAMs exist which can be used to assess hazards and risks of new chemical

substances that meet the Surfactant Criteria, including validated OECD methods for *in vitro* irritation testing, as well as other *in vitro* methods to specifically assess respiratory toxicity. Several methods are described within a tiered-testing strategy herein, but that the development of NAMs is advancing quickly. As such, the NAMs included here should not be considered all-inclusive or a final compilation. EPA strongly encourages the development and use of NAMs, particularly to reduce or replace the use of vertebrate animals and is open to considering and discussing additional NAMs with PMN submitters during a pre-notice consultation.

In the interest of reducing or replacing vertebrate testing, when a surfactant is determined to be respirable, EPA encourages evaluating its potential to cause pulmonary toxicity using an Adverse Outcome Pathway (AOP) approach. The Organization for Economic Cooperation and Development (OECD) provides "An AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect" and that "AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning" [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14798</RecNum><DisplayText>[84]</DisplayText><record><rec-number>14798</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041285">14798</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Adverse Outcome Pathways, Molecular Screening and Toxicogenomics</title><secondary-

title>Organization for Economic Cooperation and Development (OECD)</secondary-title></titles><periodical><full-title>Organization for Economic Cooperation and Development (OECD)</full-title></periodical><pages>http://www.oecd.org/env/ehs/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. Representative key elements of AOPs are the molecular initiating events (MIEs), cellular level events (CLEs), organ or tissue level events (OLEs), and organism consequent events (OCEs). For surfactants, the initial key event is proposed to be the interaction of the substance with lung-surfactant (MIE) and/or the molecular interaction of the substance itself with cell membranes (MIE), resulting in the disruption of lung cells due to loss of lung cell surfactant function (CLE) and/or the loss of membrane integrity (CLE). These initial events may lead to different OLEs (*e.g.*, alveolar collapse, loss of barrier function, blood extravasation, and impaired oxygenation of blood), which may finally lead to organism consequences (OCE) (*e.g.*, pneumonia, limited lung function by chronic obstruction (COPD), fibroses, *etc.*).

*In vitro* systems are used to investigate specific key events in the AOP and confirm that a new chemical substance fits within the boundaries of the Surfactant Category or a sub-category and therefore may act like a surfactant (group assignment *via* similar AOP) and/or if other substance specific properties lead to a predominant type of key events within the AOP. Further, *in vitro* tests may deliver information while avoiding *in vivo* testing or providing helpful information on dose-

selection for *in vivo* testing, if needed. *In vitro* tests, such as by capillary surfactometer, may be useful in preliminary screening of chemicals to be tested, but do not by themselves constitute adequate tests for acute pulmonary effects of these chemicals. This information should be taken into consideration within the design of additional *in vivo* tests. These assays can be used as part of a weight of scientific evidence evaluation to determine whether animal testing is needed or if a point of departure (POD) can be determined for risk assessment purposes without the use of animals. These tests may also provide insight on one or more components of the AOP.

Based on the surfactant AOP framework [ ADDIN EN.CITE <EndNote><Cite><Author>Sorli</Author><Year>2020</Year><RecNum>14800</RecNum>< DisplayText>[86]</DisplayText><record><rec-number>14800</rec-number><foreign- keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041625">14800</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sorli, J. B.</author></authors></contributors><titles><title>Lung Surfactant Function Disruption Leading to Acute Inhalation Toxicity</title><secondary-title>AOPWiki</secondary- title></titles><periodical><full-title>AOPWiki</full- title></periodical><pages>https://aopwiki.org/aops/302</pages><dates><year>2020</year></d ates><urls></urls></record></Cite></EndNote>], a number of different types of *in vitro* test methods, summarized in [ REF _Ref46931271 \h \* MERGEFORMAT ], may provide potentially useful information for informing the various elements of the surfactant AOP.

Table [ SEQ Table \* ARABIC ]. *In Vitro* Test Methods and New Approach Methods That May Be Useful for Evaluating Chemicals for Inclusion in Surfactant AOP and Category.

| Surfactant AOP | Information on AOP | In Vitro Assay | Test System |
|---|---|---|---|
| | MIE for interaction with pulmonary surfactant/loss of function | *In Vitro* Respiratory Toxicity Assays | • *In vitro* lung surfactant inhibition as described by Sorli *et al.* (2018) [ ADDIN EN.CITE      ADDIN EN.CITE.DATA    ] |
| *Molecular Initiating Events (MIEs)* | MIE for interaction/penetration through cell membrane | *In Vitro/Ex Vivo* Irritation Assays | • OECD *In vitro/Ex Vivo* eye irritation tests for penetrance, *e.g.*, Reconstructed human Cornea-like Epithelium (RhCE) (OECD 492) [ <br> <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[88]</DisplayText>< <br> id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Arti <br> type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like E <br> irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles>< <br> https://www.oecd-ilibrary.org/docserver/9789264242548- <br> en.pdf?expires=1596044765&amp;id=id&amp;accname=guest&amp;checksum=C972EFF7A2459C37BF048A1BDC82F2D4</page <br> Bovine Corneal Opacity and Permeability Test (OECD 437) [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year <br> number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043 <br> type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Perme <br> Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Che <br> Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846- <br> en.pdf?expires=1596044549&amp;id=id&amp;accname=guest&amp;checksum=6B06BCD6D113D26A04C508907C001D91</page <br> Isolated Chicken Eye Test (OECD 438) [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><Rec <br> number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key>< <br> type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for <br> irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles>< <br> https://www.oecd-ilibrary.org/docserver/9789264203860- <br> en.pdf?expires=1596044906&amp;id=id&amp;accname=guest&amp;checksum=37A7598040CEC8996E712477F0A603D7</pages> <br> *etc.* |
| *Cellular Level* | CLE for loss of membrane | *In Vitro/Ex Vivo* | • OECD *In vitro/Ex Vivo* eye irritation tests for cytotoxicity, *e.g.*, Reconstructed human Cornea-like Epithelium (RhCE) (OECD 492) [ <br> <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[88]</DisplayText>< <br> id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Arti |

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| Events (CLEs) | integrity/general cytotoxicity | Cytotoxicity Assays | type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like I irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><p https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&amp;id=id&amp;accname=guest&amp;checksum=C972EFF7A2459C37BF048A1BDC82F2D4</page Bovine Corneal Opacity and Permeability Test (OECD 437) [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043 type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Perm Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Che Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&amp;id=id&amp;accname=guest&amp;checksum=6B06BCD6D113D26A04C508907C001D91</page Isolated Chicken Eye Test (OECD 438) [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><Rec number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044057">14804</key>< type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Isolated chicken eye test method for irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><p https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1596044906&amp;id=id&amp;accname=guest&amp;checksum=37A7598040CEC8996E712477F0A603D7</pages> *etc.* |
| | | | <ul><li>Cell membrane integrity test (LDH-lactate dehydrogenase cytotoxicity assay), MTT assay or lysosomal membrane integrity test.</li><li>BALB/c3T3/A549 lung cells neutral red uptake (NRU) cytotoxicity test, a test for basal cytotoxicity (ICCVAM, 2006) [ ADDIN EN. <EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</RecNum><DisplayText>[91]</DisplayTex id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal Arti type><contributors><authors><author>ICCVAM</author></authors></contributors><titles><title>In vitro Cytotoxicity Test Metho title>ICCVAM Test Method Evaluation Report</secondary-title></titles><periodical><full-title>ICCVAM Test Method Evaluation https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf</pages><volume>NIH Publication No. 07-4519</li></ul> |
| Organ or Tissue Level Events (OLEs) | OLE for tissue level events | Human organotypic airway epithelial cultures | <ul><li>3-D constructs of human-derived cell cultures of differentiated airway epithelial cells (*e.g.*, EpiAirway™, MucilAir™, SmallAir™, E</li></ul> |
| | OLE for tissue level events | Specific *Ex Vivo* Respiratory | <ul><li>Precision-cut lung slice test *etc.* as described by Hess *et al.* (2016) [ ADDIN EN.CITE ADDIN EN.CITE.DATA ]</li></ul> |

[PAGE ]

| | | Toxicity Assays | |
|---|---|---|---|

*MIEs*

The surfactant AOP is hypothesized to consist of two MIEs that may be informed by *in vitro* assays to determine whether a particular chemistry causes adverse effects on the pulmonary surfactant system (MIE #1), pulmonary cell membranes (MIE #2), or both. For MIE #1, Sorli *et al.* (2017) [ ADDIN EN.CITE     ADDIN EN.CITE.DATA     ]developed an *in vitro* lung surfactant inhibition assay that specifically measures whether the substance interferes with lung surfactant function. The assay was initially benchmarked for predicting the effect of waterproofing agents that were shown to be acutely toxic to mice. The authors noted that it may be overly conservative for some substances. Nevertheless, this assay investigated a basic principle (MIE #1) which may also be relevant for some types of surfactants. For MIE #2, *in vitro* eye irritation assays represent appropriate screening approaches for determining the ability of surfactants to interact with cellular membranes and penetrate the corneal layer of the eye. For example, Bader *et al.* (2013) [ ADDIN EN.CITE

<EndNote><Cite><Author>Bader</Author><Year>2014</Year><RecNum>14807</RecNum><DisplayText>[93]</DisplayText><record><rec-number>14807</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044694">14807</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bader, J.E.</author><author>Norman, K.G.</author><author>Raabe, H.</author></authors></contributors><titles><title>Predicting Ocular Irritation of Surfactants Using the Bovine Corneal Opacity and Permeability Assay</title><secondary-title>Insitute for In Vitro Sciences, Inc., Gaithersburg, M.D.</secondary-title></titles><periodical><full-title>Insitute for In Vitro Sciences, Inc.,

Gaithersburg, M.D.</full-title></periodical><pages>https://iivs.org/wp-content/uploads/2018/08/iivs_poster_predicting-ocular-irritation-of-surfactants-using-the-bovine-corneal-opacity-and-permeability-assay.pdf</pages><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] showed that the Bovine Corneal Opacity and Permeability (BCOP) assay was effective at demonstrating that nonionic (*i.e.*, octylphenoxypolyethoxyethanol), anionic (*i.e.*, SDS), and cationic (*i.e.*, BAC) substances cause irritation to the eye; however, the authors also noted that the endpoints evaluated in this assay should be carefully assessed independently. For octylphenoxypolyethoxyethanol and SDS, the permeability score was more predictive of eye irritation than the ocular opacity score, whereas for BAC, the opacity score was more predictive of eye irritation than the permeability score. Therefore, a systematic investigation of opacity and permeability measures with surfactants using this approach may be helpful with elucidating MIE #2 of the AOP. Combining this assay with another *in vitro* test, such as LDH or MTT assay in confluent nonpolarized cells such as HeLa, which has demonstrated sensitivity for differentiating between cell membrane damage induced by different subcategories of surfactants provide an effective measure of cell membrane effects [ ADDIN EN.CITE    ADDIN EN.CITE.DATA   ].

In addition, information on the potential of a substance to cause skin irritation (*e.g.*, OECD TG 439 [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14808</RecNum><DisplayText>[94]</DisplayText><record><rec-number>14808</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596044884">14808</key></foreign-keys><ref-type name="Journal Article">17</ref-

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>Reconstructed Human Epidermis Test Method, In vitro Skin Irritation</title><secondary-
title>OECD Guidelines for the Testing of Chemicals</secondary-
title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-
title></periodical><pages>26, https://www.oecd-ilibrary.org/docserver/9789264242845-
en.pdf?expires=1596045726&amp;id=id&amp;accname=guest&amp;checksum=2580E92A5C8
89D0DD65599260E7866D3</pages><volume>439</volume><dates><year>2020</year></date
s><urls></urls></record></Cite></EndNote>]) and/or skin corrosion (*e.g.*, OECD TG 431 [
ADDIN EN.CITE
<EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14809</RecNum>
<DisplayText>[95]</DisplayText><record><rec-number>14809</rec-number><foreign-
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Article">17</ref-
type><contributors><authors><author>OECD</author></authors></contributors><titles><title
>In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test
Method</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-
title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-
title></periodical><pages>29, https://www.oecd-ilibrary.org/docserver/9789264264618-
en.pdf?expires=1596045820&amp;id=id&amp;accname=guest&amp;checksum=E3EE55CBAA
FAF0432EAD109F1B39ECF0</pages><volume>431</volume><dates><year>2019</year></d
ates><urls></urls></record></Cite></EndNote>]) *in vitro*, can provide evidence of the potential
for a substance to cause similar irritant or corrosive effects in respiratory tract cells. Corrosion

effects mediated by pH extremes should be distinguished from necrosis effects *via* membrane disruption, for example DDAC causes tissue effects in inhalation studies despite having a neutral pH value of 6.8-6.9 [ ADDIN EN.CITE <EndNote><Cite><Author>Sigma-Aldrich</Author><Year>2020</Year><RecNum>14810</RecNum><DisplayText>[96]</DisplayText><record><rec-number>14810</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045132">14810</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sigma-Aldrich</author></authors></contributors><titles><title>Safety Data Sheet, Product name: Didecyldimethylammonium chloride, Version 8.1, Revision Date: 03/28/2020, Print Date: 05/29/2020</title></titles><pages>9, https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&amp;language=en&amp;productNumber=34466&amp;brand=SIAL&amp;PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsial%2F34466%3Flang%3Den</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

## CLEs

Several *in vitro/ex vivo* assays are available that may indicate whether a new chemical substance is acting via the surfactant AOP and can be assessed within the Surfactant Category. For general cytotoxicity, the ocular irritation/corrosion studies cited in [ REF _Ref46931271 \h \* MERGEFORMAT ] provide one set of options using cell types that are known to be sensitive to the effects of surfactants. The BALB/c 3T3 NRU cytotoxicity test has been reviewed and recommended by the reviewed by the Interagency Coordinating Committee on the Validation of

Alternative Methods (ICCVAM) for use in before animal testing is conducted [ ADDIN

EN.CITE

<EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</RecNu

m><DisplayText>[91]</DisplayText><record><rec-number>14805</rec-number><foreign-

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timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal

Article">17</ref-

type><contributors><authors><author>ICCVAM</author></authors></contributors><titles><ti

tle>In vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic

Toxicity Testing</title><secondary-title>ICCVAM Test Method Evaluation Report</secondary-

title></titles><periodical><full-title>ICCVAM Test Method Evaluation Report</full-

title></periodical><pages>334,

https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-

complete.pdf</pages><volume>NIH Publication No. 07-

4519</volume><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>]

. For each assay, the surfactants with identified inhalation toxicity data that would serve as an

analogue for assessing the new chemical substance (*e.g.,* octylphenoxypolyethoxyethanol, oleoyl

sarcosine, DDAC or BAC) should be tested along with the new chemical substance to

benchmark the results, whereas nonirritating surfactants with low acute inhalation toxicity such

as Polysorbate 20 may serve as negative controls, thereby providing reliable results for

estimating the potential for surfactants to cause irritation and cytotoxicity.

*OLEs*

Based on the results of the testing on the CLEs, it may be necessary to perform more robust testing, given the limitations of these assays. For example, the discussed assays measure single cell types, whereas human and animal airway epithelia are composed of multiple cell types that each have specialized functions. Several human airway models have been developed that allow for the assessment of multiple endpoints in three-dimensional culture systems. Two commonly employed systems include EpiAirway™ and MucilAir™ developed by MatTek Life Sciences and Epithelix, respectively.

Organotypic airway epithelial cultures, such as EpiAirway™ and MucilAir™, provide a more realistic physiological *in vitro* model system than *in vitro* cell lines [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2018</Year><RecNum>14811</RecNum>< DisplayText>[97]</DisplayText><record><rec-number>14811</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596045320">14811</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Issue Paper: Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>33, https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/bcgnd-1-

epa_case_study.pdf</pages><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. Unlike single cell lines, these organotypic cultures take on a pseudostratified morphology, develop tight junctions, differentiate into multiple cell types, including: basal cells, ciliated cells, and goblet cells; generate mucus, exhibit ciliary beating, have xenobiotic metabolizing capacity, and maintain cultural homeostasis for months. Because of these characteristics, these human airway models are expected to better represent the response of *in vivo* tissue to surfactant exposure than cell line cultures of a single cell type. Depending on the level in the respiratory system where the site of contact / exposure is predicted to occur, using for example RDDR or MPPD modeling for determining deposition, different 3D cell culture systems are available that are composed of the different cell types that occur at different anatomical sites in the respiratory tract. For example, MucilAir™ provides 3D co-culture models of cells from nasal, tracheal or bronchial sites, as well as a co-culture of cells from small airways (SmallAir™). EpiAirway™ is composed of a co-culture of normal human tracheal/bronchial epithelial cells and EpiAlveolar™ is a 3D co-culture model of the air-blood barrier produced from primary human alveolar epithelial cells, pulmonary endothelial cells and fibroblasts.

Exposure to aerosols at the ALI using a Vitrocell® exposure system is a lower throughput approach to *in vitro* two-dimensional exposure systems; however, it provides an exposure more comparable exposure to real-life scenarios for inhaled aerosols. Using ALI exposure, dilution into medium and interaction with medium components does not occur as it would in a submerged culture system. There is interaction of the aerosol with a mucus or surfactant layer if organotypic cultures are used, as there would be *in vivo*, thus more physiologically relevant.

Exposures of these organotypic cultures at the ALI can be combined with a number of assays for assessing cell function and viability which inform the MIEs. Measurement of transepithelial electrical resistance (TEER), LDH-release, and viability assays such as MTT or ATP assays have all been reported for use with these cultures. Further, multiple assays can be performed on the same cultures. TEER measures epithelial integrity, including functionality of intercellular tight junctions. LDH-release measures loss of plasma membrane integrity, which is indicative of cytotoxicity, and MTT and ATP assays measure cell viability. MatTek Life Sciences recommends the MTT assay for use with their EpiAirway™ cultures and recommends the surfactant octylphenoxypolyethoxyethanol at 0.2% concentration as a positive control for cytotoxicity. These assays can also be used to determine an HEC, which may be used for quantitative risk assessment.

While significant progress has been made toward achieving the objectives to use of high-throughput *in vitro* assays and computational models based on human biology to evaluate potential adverse effects of chemical exposures [ ADDIN EN.CITE

<EndNote><Cite><Author>NRC</Author><Year>2007</Year><RecNum>14741</RecNum><DisplayText>[17, 98]</DisplayText><record><rec-number>14741</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019531">14741</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>T

oxicity Testing in the 21st Century: A Vision and a Strategy, Washington, D.C. The National

Academies Press</title></titles><pages>216, DOI:

https://doi.org/10.17226/11970</pages><volume>ISBNs: Ebook: 978-0-309-13412-5;

Paperback: 978-0-309-15173-

3</volume><dates><year>2007</year></dates><urls></urls></record></Cite><Cite><Author>

NRC</Author><Year>2017</Year><RecNum>14812</RecNum><record><rec-

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type><contributors><authors><author>NRC</author></authors></contributors><titles><title>

Using 21st Century Science to Improve Risk-Related Evaluations, Washington, D.C., The

National Academies Press</title></titles><pages>200,

https://doi.org/10.17226/24635</pages><volume>ISBNs: Ebook: 978-0-309-45351-6;

Paperback: 978-0-309-45348-

6</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>],

the investigation of effects using *in vitro* models of higher levels of biological organization

remains challenging. All other things being equal, for relevancy to humans and for animal

welfare considerations, the 3D human airway cell culture systems discussed above would be the

test systems to be aspired.


Precision-cut lung slices (PCLS) is one way to gather OLE data. The PCLS measures multiple

endpoints, such as LDH for cytotoxicity and IL-1α for pro-inflammatory cytokine release in *ex

vivo* cultures of rodent lung slices, to determine whether a chemical is likely to be toxic to the

respiratory tract by inhalation exposure [ ADDIN EN.CITE

<EndNote><Cite><Author>Liu</Author><Year>2019</Year><RecNum>14813</RecNum><D
isplayText>[99]</DisplayText><record><rec-number>14813</rec-number><foreign-keys><key
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M.</author><author>Hornberg, Jorrit J.</author><author>Sivars, Kinga
Balogh</author><author>Cohen, Taylor
S.</author></authors></contributors><titles><title>Use of precision cut lung slices as a
translational model for the study of lung biology</title><secondary-title>Respiratory
Research</secondary-title></titles><periodical><full-title>Respiratory research</full-
title><abbr-1>Respir Res</abbr-1></periodical><pages>162, https://doi.org/10.1186/s12931-
019-1131-
x</pages><volume>20</volume><number>1</number><dates><year>2019</year><pub-
dates><date>2019/07/19</date></pub-dates></dates><isbn>1465-993X</isbn><urls><related-
urls><url>https://doi.org/10.1186/s12931-019-1131-x</url></related-urls></urls><electronic-
resource-num>10.1186/s12931-019-1131-x</electronic-resource-
num></record></Cite></EndNote>]. PCLS contain intact alveoli, rather than monolayers of one
or two cells types (co-cultures). Crucially, in contrast to organoids, cell types are present in the
same ratios and with the same cell–cell and cell–matrix interactions as *in vivo*. PCLS are often
used in toxicological and anatomical studies regarding contractility in relation to asthma and
other respiratory illnesses, such as emphysema [ ADDIN EN.CITE

[PAGE  ]

<EndNote><Cite><Author>Sanderson</Author><Year>2011</Year><RecNum>14814</RecNum><DisplayText>[100]</DisplayText><record><rec-number>14814</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046031">14814</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sanderson, M. J.</author></authors></contributors><auth-address>Department of Microbiology and Physiological Systems, University of Massachusetts Medical School, Worcester, MA 01655, USA. Michael.Sanderson@umassmed.edu</auth-address><titles><title>Exploring lung physiology in health and disease with lung slices</title><secondary-title>Pulm Pharmacol Ther</secondary-title><alt-title>Pulmonary pharmacology &amp; therapeutics</alt-title></titles><periodical><full-title>Pulmonary pharmacology &amp; therapeutics</full-title><abbr-1>Pulm Pharmacol Ther</abbr-1></periodical><alt-periodical><full-title>Pulmonary pharmacology &amp; therapeutics</full-title><abbr-1>Pulm Pharmacol Ther</abbr-1></alt-periodical><pages>452-65</pages><volume>24</volume><number>5</number><edition>2011/05/24</edition><keywords><keyword>Animals</keyword><keyword>Cell Physiological Phenomena</keyword><keyword>Disease Models, Animal</keyword><keyword>Humans</keyword><keyword>Lung/pathology/*physiology</keyword><keyword>Lung Diseases/*pathology</keyword><keyword>Microscopy/methods</keyword><keyword>Muscle Contraction/physiology</keyword><keyword>Organ Culture Techniques</keyword></keywords><dates><year>2011</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>1094-5539 (Print)&#xD;1094-

5539</isbn><accession-num>21600999</accession-

num><urls></urls><custom2>PMC3168687</custom2><custom6>NIHMS296121</custom6><

electronic-resource-num>10.1016/j.pupt.2011.05.001</electronic-resource-num><remote-

database-provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>]. Therefore, physiological

responses, other than cytotoxicity, that may be evoked by the surfactant may be monitored. One

further advantage of PCLS is that the PCLS assay can be performed on multiple species to

determine inter-species variability in susceptibility.

The PCLS test system has been pre-validated in multiple, independent laboratories, and the

results showed good correlation when translated from *in vivo* $LC_{50}$ values [ ADDIN EN.CITE

ADDIN EN.CITE.DATA    ]. While considered an alternative test, this assay still requires use of

laboratory animals, albeit that, compared to *in vivo* inhalation tests, this assay reduces the

number of animals that would be needed to conduct dose response studies. From a rat lung (1 g),

about > 200 slices can be prepared. In general, for 1 concentration, 2 slices are used, resulting in

100 different concentrations or repeats that can be tested with one sacrificed rat. Additionally,

PCLS cultures are stable for up to 4 weeks and allows for exposures via media or air with

additional adaptations. As such, the PCLS system meets the goal of reducing animal testing. The

rationale for selection of the PCLS assay, as with any inhalation toxicity assay, should be

scientifically justified in advance of initiating testing.

Uncertainties/Limitations

**Commented [HT34]:** For the whole FRAMEWORK

[PAGE  ]

A number of *in vitro* assays have been discussed as to their potential utility within the context of surfactant AOP elements (*i.e.*, MIEs, CLEs, and OLEs). Uncertainties and limitations associated with these assays are discussed for each of the above testing systems, as well as others [ ADDIN EN.CITE ADDIN EN.CITE.DATA ], it is important to consider that these assays were not systematically tested using surfactants or benchmarked against *in vivo* inhalation toxicity data on surfactants. Nonetheless, these assays, alone or in combination should be considered from the point of view of providing information to determine whether a new chemical meets the Surfactant Category criteria and/or to understand whether the new chemical may be more or less bioactive or toxic than the sub-category analogue(s) currently available. In other words, absent any refining information, EPA will generally use the framework and analogue toxicity data identified in this investigation to assess potential risks from surfactants.

> **Commented [HT35]:** Maybe this goes at the very end of this section?

In this regard, approaches to evaluate the scientific confidence of test methods for hazard assessment and risk assessment have, and continue to, evolve. A fit for purpose framework, employing specific criteria to establish relevancy, reliability, variability, sensitivity, domain of applicability, *etc.*, for evaluating and documenting the scientific confidence of a new method for use for informing specific decision context has emerged from the regulatory science community to address the challenges posed for validation of NAMs that provide scientific rigor, but that are also flexible and adaptable [ ADDIN EN.CITE ADDIN EN.CITE.DATA ].

> **Commented [HT36]:** ODIN: this para needs re-write; offers no edits

Once such fit for purpose scientific confidence evaluations are documented, there are several ways that these assays can be used to avoid excessive animal testing. First, testing can be

[PAGE ]

performed on the surfactant AOP to evaluate the potency of new surfactants versus a comparator

surfactant (analogue) within the relevant subcategory that has repeated concentration inhalation

toxicity data. Second, depositional data using models such as RDDR or MPPD for determining

the depositional fraction of the new surfactant may be used for test concentration estimation and

for estimating a potency ratio. Finally, *in vitro* to *in vivo* extrapolations (IVIVEs) may be used to

determine a HEC for quantitative risk assessment.

> **Commented [OS37]:** Tala to include some additional text – read across, etc.

## Tiered-testing Strategy

> **Commented [HT38]:** DISCUSS CATEGORY CRITERIA AS FIRST STEP

A tiered testing approach for surfactants that have been established to meet the Surfactant Criteria

is discussed below. It commences with the least complex, most efficient testing methods, and the

complexity of the test system increases, commensurate with the AOP, to more effectively emulate

the biology and physiology of the *in vivo* respiratory tract system.

Tier I—Physical-chemical properties

Surfactants are proposed to cause a specific sequence of biological events in the pulmonary

region if they are respired. Manufacture, processing or use of a surfactant in a respirable form,

(*i.e.*, ≤ 10 μm) is therefore, an initial consideration of the potential for a surfactant to cause

pulmonary toxicity. Particle size is an established method for determining respirability of

particles/droplets. Several validated test methods exist for determining potential respirability,

*i.e.*, particle size, of a new chemical substance (*e.g.*, OECD GD 39 [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum>

<DisplayText>[105]</DisplayText><record><rec-number>14819</rec-number><foreign-

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timestamp="1596046851">14819</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment, No. 39 (Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</secondary-title></titles><periodical><full-title>Environment Directorate, Joint Meeting of the Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for Economic Cooperation and Development</full-title></periodical><pages>106, https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&amp;doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>], ISO 21501-1:2009 [ ADDIN EN.CITE <EndNote><Cite><Author>ISO</Author><Year>2009</Year><RecNum>14820</RecNum><DisplayText>[106]</DisplayText><record><rec-number>14820</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596046993">14820</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ISO</author></authors></contributors><titles><title>Determination of particle size distribution — Single particle light interaction methods — Part 1: Light scattering aerosol spectrometer</title></titles><pages>https://www.iso.org/standard/42728.html</pages><volume

>ISO 21501-

1:2009</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote

>], OECD TG 110 [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>14821</RecNum>

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>Particle Size Distribution/Fibre Length and Diameter Distributions; Method A: Particle Size

Distribution (effective hydrodynamic radius); Method B: Fibre Length and Diameter

Distributions</title><secondary-title>OECD Guidelines for the Testing of

Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of

Chemicals</full-title></periodical><pages>13, https://www.oecd-

ilibrary.org/docserver/9789264069688-

en.pdf?expires=1596047951&amp;id=id&amp;accname=guest&amp;checksum=A9C13F0DFD

CF2A5DD4DD39DAC64C47BC</pages><volume>110</volume><dates><year>1981</year><

/dates><urls></urls></record></Cite></EndNote>], and OPPTS 830.7520 [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>14822</RecNum><

DisplayText>[108]</DisplayText><record><rec-number>14822</rec-number><foreign-

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>P

article Size, Fiber Length, and Diameter Distribution</title><secondary-title>Product Properties

Test Guideline, Office of Pollution Prevention and Toxics, U.S. Enviornmental Protection

Agency</secondary-title></titles><periodical><full-title>Product Properties Test Guideline,

Office of Pollution Prevention and Toxics, U.S. Enviornmental Protection Agency</full-

title></periodical><pages>13, https://www.regulations.gov/contentStreamer?documentId=EPA-

HQ-OPPT-2009-0151-0030&amp;contentType=pdf</pages><volume>EPA 712-C-96-

037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]).

As a practical matter, a particle size cutoff of > 1% respirable particles/droplets by weight (wt%),

determined in a well conducted study using a valid measurement method will generally be

considered as triggering a quantitative assessment of inhalation toxicity on a new chemical

substance meeting the Surfactant Criteria. In other words, EPA will generally assess the potential

inhalation toxicity for a new surfactant chemical substance when the manufacture, processing or

use results in greater than 1% (by weight) of the surfactant particles/droplets having a particle

size of less than 10 um. This cutoff is consistent with EPA's "trace amounts" threshold for the

nonreportable content for nanoscale materials [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>14823</RecNum><

DisplayText>[109]</DisplayText><record><rec-number>14823</rec-number><foreign-

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>C

hemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting

and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

If respirable particles/droplets can be generated at greater than 1 wt% during manufacturing, processing, or any of the uses for the new chemical substance, proceed to Tier II.

> **Commented [OS39]:** Raphael: As per polymer overload, having a mg/m3 metric in addition to the 1% respirable would be helpful in certain situation e.g. very low particle/droplet emission during use so measuring 1% respirable is technically challenging or not feasible.

Tier II—*In vitro/Ex vivo* studies

The following *in vitro/ex vivo* test methods may provide potentially useful information indicating whether or not a new chemical substance invokes MIEs and CLEs. In order to determine the best approach for *in vitro/ex vivo* testing, a pre-notice consultation with EPA is highly encouraged, given that none of the following studies are validated to determine lung toxicity induced by surfactants. In general, the testing approach should include a combination of assays, such as one on "Pulmonary surfactant interaction/loss of function", one on "Cell interaction/penetration", and one on "General cytotoxicity" ([ REF _Ref46931271 \h \* MERGEFORMAT ]). The *in vitro/ex vivo* eye irritation studies may satisfy the latter two endpoints. If equivocal findings are obtained on the "Cell interaction/penetration" or "General cytotoxicity" assays, then the NRU cytotoxicity test should be performed. For each assay, the representative analogue to the new chemical substance for the respective subcategory of surfactants should be tested under identical conditions for comparison. Further, dosimetry models such as RDDR or MPPD may be applied to the new chemical substance to aid with identifying the appropriate test concentrations for the *in vitro/ex*

> **Commented [HT40]:** Needs more explanation; EPA would normally do this in assessing...if PRIMARILY for identifying app test, say that and then add in that any RDDR or MPPD modeling should be discussed at pre-submission consultation AND sent in with PMNcc

[PAGE ]

*vivo* test systems, considering for example the surface area of the culture system or *ex vivo* tissue, loss mechanisms, *etc.*

*Pulmonary surfactant interaction/loss of function*

- *In vitro* lung surfactant inhibition as described by Sorli *et al.* (2017) [ ADDIN EN.CITE ADDIN EN.CITE.DATA ]

*Cell interaction/penetration*

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.,* OECD 492 [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecNum><DisplayText>[88]</DisplayText><record><rec-number>14803</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>43, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&amp;id=id&amp;accname=guest&amp;checksum=C972EFF7A2459C37BF048A1BDC82F2D4</pages><volume>492</volume><dates><year>2019</ye

ar></dates><urls></urls></record></Cite></EndNote>]: Reconstructed human Cornea-like

Epithelium (RhCE) Test Method; OECD 437 [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14802</RecN

um><DisplayText>[89]</DisplayText><record><rec-number>14802</rec-

number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

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type><contributors><authors><author>OECD</author></authors></contributors><titles><ti

tle>Bovine Corneal Opacity And Permeability Test Method For Identifying i) Chemicals

Inducing Serious Eye Damage And ii) Chemicals Not Requiring Classification For Eye

Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing

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Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-

ilibrary.org/docserver/9789264203846-

en.pdf?expires=1596044549&amp;id=id&amp;accname=guest&amp;checksum=6B06BCD6

D113D26A04C508907C001D91</pages><volume>437</volume><dates><year>2020</yea

r></dates><urls></urls></record></Cite></EndNote>]: Bovine Corneal Opacity and

Permeability Test Method; OECD 438 [ ADDIN EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</RecN

um><DisplayText>[90]</DisplayText><record><rec-number>14804</rec-

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type><contributors><authors><author>OECD</author></authors></contributors><titles><ti

tle>Isolated chicken eye test method for identifying I) chemicals inducing serious eye

damage and II) chemicals not requiring classification for eye irritation or serious eye

damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-

title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-

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en.pdf?expires=1596044906&amp;id=id&amp;accname=guest&amp;checksum=37A759804

0CEC8996E712477F0A603D7</pages><volume>438</volume><dates><year>2018</year>

</dates><urls></urls></record></Cite></EndNote>]: Isolated Chicken Eye Test Method,

*etc*.

*General cytotoxicity*

- OECD *in vitro/ex vivo* eye irritation tests, *e.g.*, OECD 492 [ ADDIN EN.CITE

  <EndNote><Cite><Author>OECD</Author><Year>2019</Year><RecNum>14803</RecN

  um><DisplayText>[88]</DisplayText><record><rec-number>14803</rec-

  number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

  timestamp="1596043912">14803</key></foreign-keys><ref-type name="Journal

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  type><contributors><authors><author>OECD</author></authors></contributors><titles><ti

  tle>Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying

  chemicals not requiring classification and labelling for eye irritation or serious eye

  damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-

  title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-

title></periodical><pages>43, https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1596044765&amp;id=id&amp;accname=guest&amp;checksum=C972EFF7A2459C37BF048A1BDC82F2D4</pages><volume>492</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]: Reconstructed human Cornea-like Epithelium (RhCE); OECD 437 [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2020</Year><RecNum>14802</RecNum><DisplayText>[89]</DisplayText><record><rec-number>14802</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596043719">14802</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Bovine Corneal Opacity And Permeability Test Method For Identifying i) Chemicals Inducing Serious Eye Damage And ii) Chemicals Not Requiring Classification For Eye Irritation Or Serious Eye Damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>28, https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1596044549&amp;id=id&amp;accname=guest&amp;checksum=6B06BCD6D113D26A04C508907C001D91</pages><volume>437</volume><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]: Bovine Corneal Opacity and Permeability Test; OECD 438 [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14804</RecNum><DisplayText>[90]</DisplayText><record><rec-number>14804</rec-

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type><contributors><authors><author>OECD</author></authors></contributors><titles><ti

tle>Isolated chicken eye test method for identifying I) chemicals inducing serious eye

damage and II) chemicals not requiring classification for eye irritation or serious eye

damage</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-

title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-

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en.pdf?expires=1596044906&amp;id=id&amp;accname=guest&amp;checksum=37A759804

0CEC8996E712477F0A603D7</pages><volume>438</volume><dates><year>2018</year>

</dates><urls></urls></record></Cite></EndNote>]: Isolated Chicken Eye Test, *etc.*

- ICCVAM (2006) [ ADDIN EN.CITE

<EndNote><Cite><Author>ICCVAM</Author><Year>2006</Year><RecNum>14805</Re

cNum><DisplayText>[91]</DisplayText><record><rec-number>14805</rec-

number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596044231">14805</key></foreign-keys><ref-type name="Journal

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type><contributors><authors><author>ICCVAM</author></authors></contributors><titles

><title>In vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral

Systemic Toxicity Testing</title><secondary-title>ICCVAM Test Method Evaluation

Report</secondary-title></titles><periodical><full-title>ICCVAM Test Method Evaluation

Report</full-title></periodical><pages>334,

https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-complete.pdf</pages><volume>NIH Publication No. 07-4519</volume><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] recommended protocol for the BALB/c 3T3/A549 lung cells neutral red uptake (NRU) cytotoxicity test, a test for basal cytotoxicity (Appendix C1)

Acknowledging the model predictability and uncertainties, Eeach of the assays may could be used to determine a starting point to calculate a modified $POD_{HEC}$ using *in vitro* to *in vivo* extrapolation (IVIVE) for the purpose of evaluating the relative potency of the new chemical substance versus the comparator analogue. That said, a Weight of Evidence (WoE) approach should be taken giving consideration to the new substance structure/properties, the results of the assays, their biological relevance and their related uncertainties The most sensitive of the biologically relevant endpoints identified from the assays should be used to calculate a POD using BMD modeling, when possible, with the $BMCL_{1SD}$ metric. This metric is based on the benchmark response (BMR) of one standard deviation suggested for *in vitro* assays (a ~15%, 13% and 5% change from the control group values relative to the data range for the TEER, resazurin and lactate dehydrogenase assays, respectively), per the 2018 FIFRA Inhalation Scientific Advisory Panel meeting [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2019</Year><RecNum>14825</RecNum><DisplayText>[110]</DisplayText><record><rec-number>14825</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048386">14825</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Transmittal of Meeting Minutes and Final Report for the Federal Insecticide Fungicide and Rodenticide Act, Science Advisory Panel (FIFRA SAP) Meeting held on December 4 and 6, 2018</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>51,https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2018-0517-0030&amp;contentType=pdf</pages><volume>EPA-HQ-OPP-2018-0517</volume><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]. However, alternative metrics may be considered. For example, the pharmaceutical industry has used fixed adverse response thresholds that are appropriate for the specific biological assay (*i.e.*, $EC_{15}$, $EC_{30}$, *etc.*) [ ADDIN EN.CITE    ADDIN EN.CITE.DATA    ]. Regardless of the metric used, a justification for its selection should be provided. In those situations where data are not amenable to BMD modeling, the *in vitro* concentration tested should be determined based on the expected HEC for the appropriate subcategory (taking into account the necessary MOE) to ensure that the *in vitro* data are generated in a concentration range relevant to the expected HEC.

The decision to Stop at Tier II or proceed to Tier III should be based reviewing the expected MOE versus the estimated uncertainties in the new substance's estimated $POD_{HEC}$, so that the magnitude of the MOE is providing sufficient reassurance to account for the specific uncertainties of the $POD_{HEC}$. Those uncertainties were discussed previously (e.g. substance similarity, predictability/validity of the in-vitro model, consistencies of results between different models, etc.)

and should be reviewed in a WoE approach based on the any other available evidence and the latest scientific knowledge.

For example, in a situation where there would be high confidence in the $POD_{HEC}$ (e.g. new chemical similar in structure/physchem properties to the benchmark substance(s) and the outcome of the assays were consistent), a minimal standard MOE would be acceptable to stop at Tier II. Alternatively, in a case where there would be a low confidence in the $POD_{HEC}$ (e.g. new chemical not be as similar to the benchmark substance(s) and the outcome of the assays were not consistent), a larger than standard MOE would be required to Stop at II. The latter scenario is likely to reflect situation where inhalation exposures is limited, so that magnitude of the MOE is protective of the uncertainties in the $POD_{HEC}$ derivation.

Based on the results of the above testing combinations, the following outcomes are possible, noting that a positive result in one of the 3 assays, will drive the determination of "greater" or "comparable" toxicity, whereas negative results in all 3 assays will drive the determination of "lower" toxicity, as described below.

If the new chemical substance exhibits greater toxicity versus the comparator analogue, per the study method criteria, in any one of the evaluated assays, proceed to Tier III.

If the new chemical substance exhibits comparable toxicity to the comparator analogue, per the study method criteria, in any of the evaluated assays, then stop at Tier II. The analogue POD is suitable for conducting the risk assessment.

> **Commented [HT41]:** SALAZAR: NOT CLEAR WHAT THE '3' ASSAYS ARE

> **Commented [RAB42]:** Its not clear how MOE fits into these decision criteria. I inserted draft text below – highlighted -- as a suggestion – please review and revise as needed

~~If the new chemical substance exhibits lower toxicity or negative findings relative to the comparator analogue, per the study method criteria, in all the evaluated assays, then determine if a modified POD~~$_{HEC}$~~can be calculated from the representative analogue in the respective subcategory of surfactants. If a modified POD~~$_{HEC}$~~can be calculated, then recalculate the MOE using the modified POD~~$_{HEC}$~~. If risks are still identified with the modified POD~~$_{HEC}$~~, then stop at Tier II. Evaluate whether to use the analogue POD and/or modified POD~~$_{HEC}$~~for conducting the risk assessment. If it is not possible to calculate a modified POD~~$_{HEC}$~~, then use the comparator analogue for risk assessment or proceed to Tier III.~~

Tier III – Human Airway Models/PCLS Assay

Several testing options are available for evaluating OLEs in the surfactant AOP. The test system employed should focus on evaluating effects in the respiratory tract at the predicted sites of deposition (*e.g.*, TB and/or PU regions) using RDDR or MPPD modeling, as discussed previously. A justification for using a particular system(s) versus another should be provided and may be discussed with EPA as part of a pre-notice consultation. Available test systems include, but are not limited to, the following:

- EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells
- MucilAir EpiAirway™ 3-D constructs of human-derived cell cultures of differentiated airway epithelial cells
- SmallAir™ 3-D constructs of primary human small airway epithelia reconstituted *in vitro*.

[PAGE ]

- Precision-cut lung slice test *etc*. as described by Hess *et al*. (2016) [ ADDIN EN.CITE

  ADDIN EN.CITE.DATA ]


Based on the results of the 3D-construct and/or PCLS testing, *in vitro* to *in vivo* extrapolation
may be possible for developing a $POD_{HEC}$ for use with characterizing potential risks using the
MOE approach. Though the occupational/consumer exposure estimates may be the same
between Tiers II and III, the Tier III test results may offer the opportunity for refining the risk
estimates. For example, the BMR used for calculating the $POD_{HEC}$ may be refined because the
ALI-based exposure is more consistent with inhalation exposure in a human than the submerged
culture exposures employed in Tier II [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2018</Year><RecNum>14811</RecNum><
DisplayText>[97]</DisplayText><record><rec-number>14811</rec-number><foreign-
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timestamp="1596045320">14811</key></foreign-keys><ref-type name="Journal
Article">17</ref-
type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Is
sue Paper: Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of
Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)
</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S.
Environmental Protection Agency, Washington, D.C. 20460</secondary-
title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S.
Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>33,
https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/bcgnd-1-

epa_case_study.pdf</pages><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. Further, application of uncertainty factors for calculating the benchmark MOE may also be refined, if for example, human cultures are used, which may preclude the need for applying a $UF_A$.

If the Tier III test data are amenable for developing a $POD_{HEC}$, then the risk estimates should be reassessed taking into account the new substance structure/properties, the results of the assays, their biological relevance and their related uncertainties. If no risks are identified under the conditions of use, then stop at Tier III. If risks are still identified under the conditions of use, then consider engineering controls and/or appropriate PPE requirements for worker risks and/or reformulation of the new chemical substance at a lower wt% in products for consumer risks.

If the Tier III test data are not amenable for developing a $POD_{HEC}$, then proceed to Tier IV.

Tier IV—*In vivo* studies

Strategic *in vivo* testing may be needed to inform the hazard and risk assessment of new chemical substances, particularly in those instances where a new chemical substance has unique properties that preclude a determination that one of the subcategory analogues is appropriate for read across, as well as in instances where the test data generated under Tiers II and III are not amenable for deriving $POD_{HEC}$s. If *in vivo* testing is needed, a pre-notice consultation meeting with EPA is strongly encouraged prior to initiating any vertebrate animal testing. This point is especially

important because TSCA section 4(h)(3) indicates that any person developing information for submission under TSCA section 5 on a voluntary basis shall first attempt to develop the information by means of an alternative test method or strategy identified by EPA before conducting new vertebrate animal testing [ ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>14796</RecNum> <DisplayText>[82]</DisplayText><record><rec-number>14796</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596041048">14796</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S.C.</author></authors></contributors><titles><title> Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-title></titles><periodical><full-title>United States Code (U.S.C.)</full-title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53 &amp;edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

The potential for surfactants to cause adverse effects on the respiratory tract are based on acute toxicity concerns, that is, interfering with pulmonary surfactant and/or disrupting cellular membranes. Since these effects may be captured using appropriate exposure concentrations in short-term inhalation studies, the following *in vivo* tests should be considered:

- Step 1: OECD Acute TG 403 [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2009</Year><RecNum>14827</RecNum><DisplayText>[112]</DisplayText><record><rec-number>14827</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048858">14827</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Acute Inhalation Toxicity</title><secondary-title>OECD Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>19, https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg403.pdf</pages><volume>403</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] (modified)** featuring rats exposed for 4 hours and observed for 2 weeks using aerosol exposure.

- Step 2: 5-Day inhalation study with a 14-day recovery period** to address progression of effects (use OECD TG 412 [ ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14828</RecNum><DisplayText>[113]</DisplayText><record><rec-number>14828</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048957">14828</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles

><title>28-day (subacute) inhalation toxicity study</title><secondary-title>OECD

Guidelines for the Testing of Chemicals</secondary-title></titles><periodical><full-

title>OECD Guidelines for the Testing of Chemicals</full-title></periodical><pages>23,

https://doi.org/10.1787/9789264070783-

en</pages><volume>412</volume><dates><year>2018</year></dates><urls></urls></r

ecord></Cite></EndNote>], but conduct exposure duration for at least 5 days).

**Modifications to all of the above studies should (if measurable) include pulmonary function

testing, analysis of BALF, LDH release, blood oxygen ($pO_2$) content, and satellite reversibility.

OECD      TG      412      and      OECD      GD      39      [      ADDIN      EN.CITE

<EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>14819</RecNum>

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Article">17</ref-

type><contributors><authors><author>OECD</author></authors></contributors><titles><title

>Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment, No. 39

(Second Edition)</title><secondary-title>Environment Directorate, Joint Meeting of the

Chemicals Committee and The Working Party on Chemicals, Pesticides and Biotechnology,

Organization      for      Economic      Cooperation      and      Development</secondary-

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Committee and The Working Party on Chemicals, Pesticides and Biotechnology, Organization for

Economic          Cooperation          and          Development</full-title></periodical><pages>106,

https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)2 8/rev1&amp;doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><d ates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] should be consulted. Additionally, the sensory irritant potential can be measured using ASTM E 981 to determine reflex inhibition [ ADDIN EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>2001</Year><RecNum>14826</RecNum> <DisplayText>[114]</DisplayText><record><rec-number>14826</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596048712">14826</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Alarie, Y.</author><author>Nielsen, G.D.</author><author>Schaper, M.M.</author></authors><secondary-authors><author>Spengler, B.</author><author>Samet, J. M.</author><author>McCarthy, J.F.</author></secondary-authors></contributors><titles><title>Animal Bioassays for Evaluation of Indoor Air Quality</title><secondary-title>Indoor Air Quality Handbook</secondary-title></titles><pages>23.21- 23.49.</pages><dates><year>2001</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill</publisher><urls></urls></record></Cite></EndNote>].

The results of the *in vivo* testing should be used for reassessing and recharacterizing the risks estimated using a surfactant analogue chemical.

## CONCLUSIONS

Commented [ST43]: Needs some work

[PAGE ]

The overall objective of this investigation was to develop a chemical category for use in conducting inhalation risk assessment for new chemical surfactant substances under TSCA. This investigation provides physical-chemical properties, *i.e.*, the Surfactant Criteria, assessors can use for determining whether a new chemical substance can be considered a surfactant. Further, properties and characteristics are provided to divide the surfactant category into sub-categories for nonionic, anionic and cationic surfactants, which is important from a toxicological perspective. A systematic literature search and review were conducted to identify data to define a surfactant category and toxicological analogues from read-across could be performed. Animal toxicity studies that could be used to derive PODs for risk assessments were identified for at least one analogue for each sub-category. EPA recommended duration and dosimetric adjustment factors to these toxicity studies to derive HECs for each subcategory. Finally, a tiered-testing strategy is provided that focuses on integrating a variety of NAMs currently available. Integrating NAMs into the category testing approach not only supports EPA and TSCA goals of reducing and replacing vertebrate animal testing, but also serves to encourage development of mechanistic data to advance understanding of inhalation adverse outcome pathway and toxicity of surfactants.

**ASSOCIATED CONTENT**

(Word Style "TE_Supporting_Information"). **Supporting Information**. A listing of the contents of each file supplied as Supporting Information should be included. For instructions on what should be included in the Supporting Information as well as how to prepare this material for publications, refer to the journal's Instructions for Authors.

The following files are available free of charge.

brief description (file type, i.e., PDF)

brief description (file type, i.e., PDF)

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**Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

**Notes**

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

## ACKNOWLEDGMENT

[PAGE  ]

Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).

**REFERENCES**

[ ADDIN EN.REFLIST ]

**From:** Stephanie Snyder [stephanie.snyder@covestro.com]
**Sent:** 7/31/2020 4:26:24 AM
**To:** Stedeford, Todd [Stedeford.Todd@epa.gov]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Salazar, Keith [Salazar.Keith@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]
**Subject:** RE: revised draft for polymer lung overload + supporting information file
**Attachments:** Draft manscript insoluble polymers and lung overload - 30 July 2020.ver.1.docx

Hi Todd,

# Ex. 5 Deliberative Process (DP)

No additional comments on the supporting information file.

Thanks,
Stephanie

**From:** Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
**Sent:** Thursday, July 30, 2020 7:07 PM
**To:** Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael; Ladics, Greg; Ogden, Julianne; Stephanie Snyder; Tveit, Ann; Irwin, William; Salazar, Keith; Henry, Tala
**Subject:** revised draft for polymer lung overload + supporting information file
**Importance:** High

All,

Please find the attached, revised draft of the lung overload manuscript and the supporting information file for our call tomorrow. I kept all changes in track changes, so you can see the updates based on edits/comments received to date.

Thanks,


Todd

# Polymer Lung Overload Category: The Application of a New Approach Methodologies Methodology (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

Todd Stedeford[a,*], Gregory S. Ladics[b], Owen Price[c], Annie Jarabek[d], Ann Tveit[e], Michael P. Hayes[f], Raphaël T. TremblayRaphael Tremblay[f], Stephanie A. Snyder[g], Keith Salazar[h], Sahar Osman-Sypher[i], William Irwin[h], Marc Odin[i], Julie Melia[j], Heather Carlson-Lynch[j], and Tala R. Henry[a]

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## ABSTRACT

Poorly soluble and non-reactive high-molecular weight (HMW) polymers ($\geq$10,000 Daltons)

represent a generic category of substances that are extensively used in industrial and consumer

applications (*e.g.*, plastics). Under the 2016 amended Toxic Substances Control Act (TSCA),

HMW polymers may qualify for an exemption from the pre-notification requirements that exist

for polymeric, new chemical substances. However, for HMW polymers that do not meet the

exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental

Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload.

In the present evaluation, a systematic review of the literature was performed to identify studies

that would aid with defining key properties for determining whether respirable HMW polymers

may present an unreasonable risk to human health. These properties included: respirability,

reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for ~~several~~ a toxicological analogues that ~~can~~ may be used as a first step in risk assessments on these substances. Finally, a tiered-testing strategy was developed as a new approach method that maximizes the use of non-vertebrate testing ~~(i.e., NAMs) was developed~~ that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

## INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law on June 22nd, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1. The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));

2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));

3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));

4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or

5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, "up-front" testing requirements (*e.g.*, the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA ), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><Dis

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environmental effects of a substance</title><secondary-title>Code of Federal

Regulations</secondary-title></titles><periodical><full-title>Code of Federal

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urls><url>https://www.law.cornell.edu/cfr/text/40/720.50</url></related-

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EPA's New Chemicals Program (NCP) has historically used various approaches to evaluate the
potential hazards of new chemical substances including the use of computational toxicology
models and analogue and category approaches to "read-across" from existing data to new
chemical substances for various requisite extrapolations. EPA's TSCA New Chemicals Program
(NCP) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on
specific chemical definitions and categorical boundaries that summarize the hazard concerns
(*e.g.*, human health or environmental toxicity) and recommend testing that may be conducted
prior to submitting a new chemical substance notification [ ADDIN EN.CITE

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SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of

Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</full-

title></periodical><pages>https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>201

0</year></dates><urls></urls></record></Cite></EndNote>].

Although the NCP Chemical Categories document provides transparency to the regulated

community on the potential concerns that EPA may have for hazards of specific chemistries or

physicochemical propertiesto the regulated community on the potential concerns that EPA may

have for hazards of specific chemistries or physical properties, the NCP Chemical Categories

were developed prior to the enactment of the amendments to TSCA, and therefore, do not reflect

new vertebrate testing reduction goals [ ADDIN EN.CITE

<EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>79</RecNum><Di

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&amp;edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cit

e><Cite><Author>Wheeler</Author><Year>2019</Year><RecNum>80</RecNum><record><

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A.R.</author></authors></contributors><titles><title>Directive to Prioritize Effects to Reduce

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Protection Agency</full-title></periodical><pages>3,

https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-

231249.pdf</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndN

ote>]. For example, the testing strategy in the NCP Chemical Categories document for

respirable, poorly soluble particulates[1] includes ~~vertebrate animal testing, such as~~ a 90-day

subchronic inhalation toxicity study in rats with a 60-day recovery period [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><Dis

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[1] EPA identified particles as "respirable" to humans "if there are any particles $\leq 10$ μ[m] in
diameter [not otherwise specified, e.g., physical or aerodynamic] in the material being handled
by workers" and included "poorly soluble" compounds citing ILSI (2000) [56].

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Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has also developed exemption criteria for specific types of polymeric substances, based on its findings that they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption", for specific types of polymeric substances [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><Dis

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remanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final

Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-

title>Federal Register</full-title></periodical><pages>16316-

16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dat

es><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria

are exempt from the new chemical substance notification requirements, although there are still

~~some requirements, including~~ annual reporting and recordkeeping requirements [ ADDIN

EN.CITE

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0 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-

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ar>2020</year></dates><urls></urls></record></Cite></EndNote>].

EPA's polymer exemption established three polymer exemption types, designated as E1, E2, and E3. The general criteria for new chemical polymer substances meeting these exemption types for polymers are shown in [ REF _Ref46665925 \h \* MERGEFORMAT ].

**Table [ SEQ Table \* ARABIC ].** EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

| Exemption Type[a,b] | Number-average molecular weight (NAMW) | Oligomeric Material Criteria | Functional Groups (FGs)[c] and Functional Group Equivalent Weight (FGEW) Content |
|---|---|---|---|
| E1 | 1,000 ≤ NAMW < 10,000 | < 10 wt% below 500 Daltons < 25 wt% below | Low concern FGs:[c] no limit<br>Moderate-concern FGs: FGEW ≥ 1,000<br>Moderate-concern FGs + High concern FGs: FGEW$_{combined}$ ≥ 5,000<br>High-concern FGs: FGEW ≥ 5,000 |

[PAGE ]

| | | | |
|---|---|---|---|
| | | 1,000 Daltons | |
| E2 | NAM W ≥ 10,000 | < 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons | No FG restrictions |
| E3 | No limit | No limit | Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] |

a See 40 CFR § 723.250(b) Polymers. "Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units." [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

b The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ ADDIN EN.CITE

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te>]; Polymers which degrade, decompose, or depolymerize, see 40 CFR § 723.250(d)(3) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-

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title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNo

te>]; Polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory, see 40 CFR § 723.250(d)(4) [ ADDIN

EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-

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keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR §

723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-

title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNo

te>]; Water absorbing polymers with NAMW $\geq$ 10,000 Daltons, see 40 CFR § 723.250(d)(5) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 -

Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

c "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[7]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification

Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-

title>Federal Register</full-title></periodical><pages>16316-

16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

~~As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption".~~[ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]~~; however, t~~There are instances, however, where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc.*, in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather ~~are based~~ on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW $\geq$ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, $\leq$ 10 μm) represent a ~~general~~ class of chemical substances (hereinafter referred to as "HMW polymers") that may cause ~~an~~potential inhalation ~~toxicity~~ hazards, including~~(*i.e.*,~~ lung overload[2]~~)~~ *via* ~~the~~ a

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[2] Overload is defined in this article as when the exposure concentration is sufficiently high or the duration sufficiently long to overwhelm AM-mediated clearance.

specific mode~~(s)~~ of action (*i.e.*, impairment of alveolar-macrophage [AM] mediated clearance), as identified in rat inhalation studies, ~~to~~ within chemical substances present in the respirable, poorly soluble particulates ~~in the~~ NCP Chemical Categor~~ies document for respirable, poorly soluble particulates~~y. The focus on overload has been due to the fact that poor soluble particles appear to produce lung tumors in rats when AM-mediated clearance is over-whelmed and chronic inflammation is present. However, the chemical substances that are provided as analogues ~~within the boundaries for the~~ within the boundaries for the NCP Chemical Category on respirable, poorly soluble particulates are limited to discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for ~~those~~ polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as ~~representative~~ a first step with ~~toxicological analogues with~~identifying points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. ~~An additional aim was to introduce~~In addition, a new approach ~~methodologies~~ methodology (NAMs) ~~was~~ introduced as a~~the~~ tiered-testing strategy ~~to~~ that meets the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

## MATERIALS AND METHODS

### Systematic Literature Review

An initial literature search was conducted in November 2016, and a supplemental literature

search was conducted in April 2018. The details of these reviews, including the search strategies,

search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO)

criteria used for reviewing results for relevance are provided in the Supporting Information file at

"Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies

that evaluated potential "lung overload" toxicity, *i.e.*, respiratory tract toxicity of HMW

polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and

alveolar regions) effects in laboratory animals and identified points of departure, or informed the

mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this

evaluation, "lung overload" refers to the "type of retained lung burden seen with excessively

high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated

particle clearance" [ ADDIN EN.CITE

<EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><Di

splayText>[8]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key

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type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-

address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research

Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of

particles in laboratory animals and humans in relationship to issues surrounding lung overload

and human health risk assessment: a critical review</title><secondary-title>Inhal

Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-

periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>19-

57</pages><volume>12</volume><number>1-

2</number><edition>2000/03/15</edition><keywords><keyword>Air Pollutants/*adverse

effects/pharmacokinetics</keyword><keyword>Air Pollutants, Occupational/*adverse

effects/pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Animals,

Laboratory</keyword><keyword>Body Burden</keyword><keyword>Dose-Response

Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug

effects/metabolism</keyword><keyword>Pneumoconiosis/*etiology/metabolism</keyword><k

eyword>Risk Assessment</keyword><keyword>Species

Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-

Feb</date></pub-dates></dates><isbn>0895-8378 (Print)&#xD;0895-8378</isbn><accession-

num>10715617</accession-num><urls></urls><electronic-resource-

num>10.1080/089583700196536</electronic-resource-num><remote-database-

provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>]. Since "overload" is ~~defined~~

~~manifest~~ differently in experimental animals versus humans [ ADDIN EN.CITE     ADDIN

EN.CITE.DATA    ], the literature searches used search strings that were intended to be overly

inclusive to identify studies that evaluated "overload" in both experimental animals and humans.

A secondary objective was to ~~identify develop potential NAMs that may be incorporated into~~ a

tiered-testing strategy that minimizes the use of vertebrate animals and can serve as a NAM for

this chemical category.

**Risk Assessment Approaches Under TSCA**

EPA generally uses ~~the~~ a margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments ~~performed~~ on new chemical substances ~~under TSCA~~. The MOE ~~approach~~ is calculated based on a point(s) of departure (POD) divided by ~~a~~ the human exposure estimate(s). The POD is ~~typically identified~~ developed from an effect level ~~from a study(ies) in experimental animals~~ (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or by performing benchmark dose modeling ~~benchmark dose [BMD])~~ [ ADDIN EN.CITE

&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;EPA&lt;/Author&gt;&lt;Year&gt;2002&lt;/Year&gt;&lt;RecNum&gt;46&lt;/RecNum&gt;&lt;DisplayText&gt;[14, 15]&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;46&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591"&gt;46&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;EPA&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;A Review of the Reference Dose and Reference Concentration Processes&lt;/title&gt;&lt;secondary-title&gt;Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460&lt;/secondary-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460&lt;/full-title&gt;&lt;/periodical&gt;&lt;pages&gt;192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf&lt;/pages&gt;&lt;volume&gt;EPA/630/P-02/002F&lt;/volume&gt;&lt;dates&gt;&lt;year&gt;2002&lt;/year&gt;&lt;/dates&gt;&lt;urls&gt;&lt;/urls&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;Cite&gt;&lt;Author&gt;EPA&lt;/Author&gt;&lt;Year&gt;2012&lt;/Year&gt;&lt;RecNum&gt;49&lt;/RecNum&gt;&lt;record&gt;&lt;rec-number&gt;49&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-

id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. An ~~duration~~ adjustment is applied to the POD to account for the exposure conditions under evaluation (*e.g.*, workers = 8 hours/day, 5 days/week) versus the exposure conditions ~~employed~~ in the experimental study (*e.g.*, 6 hours/day, 5 days/week). The human exposure estimate is typically generated ~~for new chemical substances~~ using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as acute potential dose rates (PDRs) ~~in mg/day~~ or lifetime average daily doses (LADDs) ~~in mg/kg-bw/day~~. Given that most new chemical substances ~~will~~ usually do not have occupational exposure monitoring data, ~~except for possible monitoring data on analogues,~~ the PDR is ~~typically~~ used as an initial conservative exposure estimate when calculating the MOE. For chemical substances ~~used~~ in a powder or particulate form, the ~~general~~ default PDR values for respirable ~~or~~ and total particulates are 50 mg/day (*i.e.*, 5 mg/m$^3$) ~~or~~ and 150 mg/day (*i.e.*, 15 mg/m$^3$), respectively [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>44</RecNum><Dis

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>C

hemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental

Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental

Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-

title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S.

Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-

title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></reco

rd></Cite></EndNote>]. However, for chronic effects ~~like~~ including lung overload, the LADD

represents the more appropriate exposure metric for quantifying potential risks [ ADDIN

EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><Dis

playText>[17]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>I

nterpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable

Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and

Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</full-title></periodical><pages>20, htttps://www.epa.gov/sites/production/files/2015-

05/documents/05-

iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record>

</Cite></EndNote>]. A summary of the default values used ~~for~~ in calculating PDRs and LADDs

for new chemical substances in powder or particulate form is provided in [ REF _Ref46666189

\h \* MERGEFORMAT ].


Table [ SEQ Table \* ARABIC ]. Default values used for calculating the PDR and LADD.

| Description | Equation | Parameter | Defaults | Units |
|---|---|---|---|---|
| PDR (mg/day) | $Cm \times b \times h$ | Mass concentration of chemical in air (Cm) | 5 | $mg/m^3$ |
| | | Volumetric inhalation rate (b) $(0 < b \leq 7.9)$ | 1.25 | $m^3/hr$ |
| | | Exposure duration (h) $(0 \leq h \leq 24)$ | 8 | hrs/day |
| LADD[a] (mg/kg-bw/day) | $(I \times ED \times EY) / (BW \times ATc \times 365 \text{ days/yr})$ | Inhalation PDR (I) | 50 | mg/day |
| | | Days exposed per year (ED) $(0 \leq ED \text{ (integer)} \leq 365)$ | 250 | days/site-yr |
| | | Years of occupational exposure (EY) $(0 \leq EY)$ | 40 | years |
| | | Body weight (BW) $(0 \leq ATc)$ | 80 | kg |
| | | Averaging time over a lifetime (chronic) $(0 \leq ATc)$ | 70 | years |

For each of the MOEs calculated ~~herein~~in this article, both the PDR and LADD have been provided ~~are provided~~ for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE is higher than the benchmark MOE, the ~~risks are not considered a concern under TSCA~~chemical substance is considered as not posing a potential risk.

### Benchmark MOE Derivation

The benchmark MOE ~~is derived to~~ accounts for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192,

https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability (*i.e.*, human-to-human variability or $UF_H$), interspecies variability (*i.e.*, animal-to-human extrapolation uncertainty or $UF_A$), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No Observed Adverse Effect Concentration [NOAEC] or $UF_L$). The default UF values used for calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times UF_A \times UF_L = 1000$). EPA has developed guidance ~~focused on improving~~to improve the science underlying the animal-to-human uncertainty factor, which provides generalized procedures for deriving dosimetric adjustment factors (DAF), which are applied to adjust exposure levels of observed toxicity in the animals and perform interspecies extrapolation [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 18]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-

final.pdf</pages><volume>EPA/630/P-

02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><

Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-

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Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</secondary-

title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>]. As described below in the section on interspecies extrapolation and overload simulations.

Application application of DAFs to the animal airborne exposure values yields estimates of the

concentration that would result in the same concentration to in humans, that is, the Human

Equivalent Concentration (HEC). For studies reporting with only a LOAEC, EPA recommends

benchmark dose modeling be performed, if the experimental data are amenable, to identify a

benchmark dose lower limit value (BMDL), as described in the next section, and thereby reduce

the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with

their potential applicability to the available studies that evaluated lung overload from HMW polymers.

## Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software (BMDS) is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not available in a study, EPA typically applies a $UF_L$ of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the $UF_L$ may be reduced from 10 to 1. The statistical lower confidence limit on the concentration at the BMD (i.e. because the BMDL) is a dose level corresponding to specific response levels near the low end of the observable range of the data that and incorporates and conveys more

[PAGE ]

information than the NOAEC or the LOAEC [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><Dis

playText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B

enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460</secondary-

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Agency, Washington, DC 20460</full-title></periodical><pages>99,

https://www.epa.gov/sites/production/files/2015-

01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-

12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote

>]. EPA's BMD software (BMDS, ver. 3.1.1) was used for dose-response modeling of

dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were

considered. A benchmark response (BMR) of 10% extra risk was selected, model fit evaluated

using the $\chi2$ goodness-of-fit p-value (p > 0.1), magnitude of scaled residuals at concentrations

near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from

the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all

models providing adequate fit, per EPA's guidance [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><Dis

playText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

### *Interspecies Extrapolation and Dosimetry Simulations Demonstrating Overload*

It has long been recognized that the external exposure concentration of particles is not the same amount that is inhaled, subsequently deposited and retained, and responsible for potential adverse health effects. Inhaled dose is dictated by particle inhalability and deposition mechanisms that can display regional and anatomical differences in the respiratory tract of experimental animals and humans at different ages relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and as well interact with by key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the

> **Commented [JA2]:** Needed context for why the two models were being used and to connect with the benchmark MOE section. Otherwise really hard to follow.

> **Commented [ST3R2]:** Note, Annie added this section. I accepted it, so you could see any edits, I may make

integrated processes of inhalability, deposition, and clearance. -Dosimetry[3] models have been used for decades to describe the physicochemical and biological determinants of aerodynamic behavior and toxicological responses of inhaled particles. -Such models are applied to account for species differences in the complex interactions among the described physicochemical, anatomical and physiological factors to determine inhaled dose metrics relevant to the mode of action (MOA) [ ADDIN EN.CITE

<EndNote><Cite><Author>Jarabek</Author><Year>2005</Year><RecNum>81</RecNum><DisplayText>[19]</DisplayText><record><rec-number>81</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1596125766">81</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Jarabek, A. M.</author><author>Asgharian, B.</author><author>Miller, F. J.</author></authors></contributors><auth-address>National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA.</auth-address><titles><title>Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP)</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>317-34</pages><volume>17</volume><number>7-8</number><edition>2005/07/16</edition><keywords><keyword>Air

_____

[3] Dosimetry refers to measuring or predicting the amount (*e.g.*, mass, surface area or number) of particles in a specific region of the respiratory tract at a particular point in time. Dose metrics, *e.g.*, deposited or retained mass in a specific region of the respiratory tract normalized to its surface area for portal-of-entry effects, should be constructed to correspond to the MOA of the particle and the observed toxic effect of interest.

Pollutants/*toxicity</keyword><keyword>Animals</keyword><keyword>Humans</keyword>
<keyword>*Inhalation Exposure</keyword><keyword>*Models,
Theoretical</keyword><keyword>Particle Size</keyword><keyword>Reference
Values</keyword><keyword>Reproducibility of Results</keyword><keyword>Risk
Assessment</keyword><keyword>Toxicity
Tests</keyword></keywords><dates><year>2005</year><pub-dates><date>Jun-
Jul</date></pub-dates></dates><isbn>0895-8378 (Print)&#xD;0895-8378</isbn><accession-
num>16020031</accession-num><urls></urls><electronic-resource-
num>10.1080/08958370590929394</electronic-resource-num><remote-database-
provider>NLM</remote-database-
provider><language>eng</language></record></Cite></EndNote>]. -Herein, we explore two
different available dosimetry models and conduct simulations to demonstrate factors determining
overload.


### *Regional ~~Dose-Deposited Dosimetry-Dose~~ Ratio (RDDR) Model (U.S. EPA, 1994)*

EPA introduced formal dosimetry modeling into its derivation procedures for risk assessment of
inhaled materials with its ~~EPA may apply DAFs to PODs identified from experimental animal~~
~~studies based on the methods described in its~~ 1994 ~~guidance~~ document ~~entitled titled~~ "*Methods
for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*"

[ ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><Dis
playText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. ~~When applied~~As described above, EPA may apply DAFs to PODs identified from experimental animal studies to calculate an HEC. When applied, the default DAF accounts for the toxicokinetic component of the $UF_A$ and ~~it~~ is ~~thereby~~ reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, ~~since~~ the POD is dosimetrically adjusted to a $POD_{HEC}$ ~~, whereas~~and the ~~remaining~~ $UF_A$ value of approximately 3 accounts for the toxicodynamic component of the $UF_A$. ~~Dosimetry or physiologically-based pharmacokinetic models are preferred to the default models when they are available.~~[ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title> Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</secondary-

title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental

Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-

11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-

90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNot

e>].

To derive a DAF for particle exposures, EPA developed a software program for calculating the

regional deposited dose ratio (RDDR), ~~that is, as~~ the DAF for insoluble particles. The RDDR is

an empirical model of deposition, ~~that is~~ applicable to particles in the size range of 0.5-30 μm

and calculates an RDDR ~~value~~ as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute

volume ($V_E$; mL/min), depositional fraction (Fr) ~~of the particulate in the~~ of the particle in the

regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a

normalizing factor (NF), such as respiratory tract surface area of the region with the observed

toxicity for portal-of-entry effects, ~~for the region of interest~~. The RDDR ~~user~~ inputs include mass

median aerodynamic diameter (MMAD), geometric standard deviation (σ) ~~for the particle of~~

~~interest~~, and the average bodyweight of the animal ~~used in the study~~ from which default $V_E$ and

surface areas of the respiratory tract regions ~~for the animal~~ are calculated. Human ventilatory parameters and assumptions regarding exposure regimen (*e.g.*, hours/day and lifetime) are analogously used in the model to predict the human deposition fraction with default values for the NF. The RDDR ~~may be~~is applied to the ~~duration~~ duration-adjusted POD, which describes the ~~; however, risk assessments performed under TSCA apply the RDDR to the POD obtained under the~~ laboratory animal regimen, to arrive at the POD$_{\text{HEC}}$. Thereafter, the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ ADDIN EN.CITE

<EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[20]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>DOSBox</author></authors></contributors><titles><title>DOSBox &quot;Way more FPA than Counterstrike !&quot;</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>].


### *Multiple-Path Particle Dosimetry (MPPD)* Model

~~Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation~~

~~tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.~~

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ ADDIN EN.CITE

<EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum><DisplayText>[21]</DisplayText><record><rec-number>73</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839173">73</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anjilvel, S.</author><author>Asgharian, B.</author></authors></contributors><auth-address>Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the Society of Toxicology</alt-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>41-50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keywords><keyword>Airway Resistance/physiology</keyword><keyword>Animals</keyword><keyword>Bronchi/anatomy &amp; histology/physiology</keyword><keyword>Lung/*anatomy &amp;

histology/physiology</keyword><keyword>Particle

Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function

Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal

Volume/physiology</keyword><keyword>Trachea/anatomy &amp;

histology/physiology</keyword></keywords><dates><year>1995</year><pub-

dates><date>Nov</date></pub-dates></dates><isbn>0272-0590 (Print)&#xD;0272-

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num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-

provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.*

(2016) [ ADDIN EN.CITE

<EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><Di

splayText>[22]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key

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timestamp="1595838679">70</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Miller, F. J.</author><author>Asgharian,

B.</author><author>Schroeter, J.D.</author><author>Price,

O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple

Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-

title></periodical><pages>14-

26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record><

/Cite></EndNote>] is a mechanistic, multipath model that ~~was modified and~~can be used to

predict deposition, clearance, and retained lung burden over the course of a long-term exposure ,
as described by Ladics *et al.* (2020) [ ADDIN EN.CITE

<EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><Di
splayText>[23]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-
type><contributors><authors><author>Ladics, G.</author><author>Price,
O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson,
S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry
Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide
Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-
title></titles><periodical><full-title>Chemical Research in Toxicology</full-
title></periodical><pages>In
preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndN
ote>]. The MPPD model is supported by Applied Research Associates, Inc. (ARA) and is
available as freeware. An EPA version of MPPD is anticipated to undergo external peer review
for application to Agency assessments late FY20. As with the RDDR ~~outputs~~model, the MPPD
~~outputs~~ model provides ~~values~~ predictions that may be used to calculate a $POD_{HEC}$ for inhaled
deposited dose; however, unlike the RDDR model, the MPPD model additionally provides
~~outputs~~predictions of retained dose that may be more appropriate to characterize chronic effects.
~~used to characterize acute exposures~~ *~~via~~* ~~deposition and subchronic/chronic exposures~~ *~~via~~*
~~retained dose.~~The MPPD model also incorporates inhalability[4], covers a wider size range of

[4] Inhalability can be defined as the probability that a particle of a given size will actually enter one of the

particles (0.01 – 100 μm), and has other added capabilities including the ability to construct simulations of activity patterns with different ventilation parameters within a given day.

To calculate clearance and thereby retained dose, The the MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title> Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models,

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respiratory tract orifices in the case of non-human primates or humans or enter the nares in the case of rodents that are obligatory nose breathers. Inhalability varies between species and is a critical adjustment for interspecies extrapolation.

Theoretical</keyword><keyword>Neoplasms, Radiation-

Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation

Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation

Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory

System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract

Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</

year></dates><isbn>0146-6453 (Print)&#xD;0146-6453</isbn><accession-

num>7726471</accession-num><urls><related-

urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-

urls></urls><remote-database-provider>NLM</remote-database-

provider><language>eng</language></record></Cite></EndNote>]. These rates are considered

representative of insoluble particles. More recently, the ICRP model and clearance rates have

been updated based on improved lung burden data [ ADDIN EN.CITE ADDIN

EN.CITE.DATA ]. Refinements may be imparted by chemical-specific dissolution data and

exploration of these new model values. Hygroscopic growth is currently not addressed in either

the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers.

In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar

clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar

clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-

week rat exposures. In humans, MPPD implements the ICRP clearance model localized for

individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model

are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates

associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human

[PAGE ]

model. Additional uncertainty in the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

*Benchmark Dose Modeling*

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach, as discussed in EPA (2012) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><Dis
playText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-
type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B
enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.
Environmental Protection Agency, Washington, DC 20460</secondary-
title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection
Agency, Washington, DC 20460</full-title></periodical><pages>99,
https://www.epa.gov/sites/production/files/2015-
01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-
12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote
>]. When a NOAEC is not identified in a study, EPA typically applies a UF$_L$ of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF$_L$ may be reduced from 10 to 1, because the BMDL is a dose level corresponding to specific

response levels near the low end of the observable range of the data and incorporates and conveys more information than the NOAEC or the LOAEC [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous (e.g., lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, and model fit was evaluated using the χ2 goodness-of-fit p-value (p > 0.1), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>B

enchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S.

Environmental Protection Agency, Washington, DC 20460</secondary-

title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection

Agency, Washington, DC 20460</full-title></periodical><pages>99,

https://www.epa.gov/sites/production/files/2015-

01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-

12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote

>].

## RESULTS AND DISCUSSION

### Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract

screening, 28 articles were selected for full text review, and 23 articles were identified using

additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review,

only 24 articles contained relevant information that satisfied the PECO criteria for lung overload

from HMW polymers. In the supplemental literature search, 1218 articles were identified on

PubMed and Embase (combined). Title and abstract screening resulted in 46 potentially relevant

articles for full text screening. Of these, 13 were identified as potentially relevant for review;

seven of the 13 articles were also identified in the initial literature search. Complete details on the

systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries, to develop the health effects summaries in the section on Hazard Identification, and to identify NAMs to include in the section on Tiered-Testing Strategies.

**Category Boundaries**

The category boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed further below.

It should be noted that even if a HMW polymer satisfies the ~~category~~ boundary criteria for the category, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

In humans, ~~Respirable~~ respirable particles are those chemical substances with an aerodynamic particle size of less than or equal to 10 μm. The cutoff of 10 μm, as defined by EPA in its "*Air Quality Criteria for Particulate Matter*", represents "particles collected by a sampler with an upper 50% cut point of 10 μm $D_a$ [aerodynamic diameter] and a specific, fairly sharp, penetration curve" [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[26]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndN

ote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 μm diameter that are excluded from the 10 μm $D_a$ fraction [

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<EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[26]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].

In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size cuts of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 μm $D_a$ particles as an upper limit for particles with this size entering the alveolar region [

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[PAGE  ]

<EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><
DisplayText>[27]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
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type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title
>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-
title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures
Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American
Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed.
Vincent, J.H.</full-title></periodical><pages>240,
https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-
particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-
5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>].
Further, consideration must also be given to the particle settling that may occurrate. For example,
iIn still air, 10 μm spherical particles with a density of 1 g/cm$^3$ can remain airborne for
approximately 8 minutes [ ADDIN EN.CITE
<EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><Di
splayText>[28]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key
app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"
timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-
type><contributors><authors><author>Baron,
P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne
Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute

for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].~However,~ and as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 μm particles to settle in still air) [ ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[27, 28]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>].
Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. ~~Though~~ Although occupational monitoring data provide ~~the most direct~~ assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and ~~the reality~~ that ~~nearly all~~ solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion.

For the purposes of defining this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc.*, in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 μm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, ~~a practical cutoff of >~~materials that

contain greater than or equal to 1% respirable particles by weight (wt%) based on particle size distribution data is the practical ~~as the~~ cutoff for assessing respirable particles and ~~this percentage would be based on particle size distribution data for the material. The practical cutoff of ≥ 1 wt%~~ is the same cutoff EPA applies to the nonreportable content of nanoscale materials [ ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><DisplayText>[29]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ~~This~~ The same cutoff would apply to the particle/droplet size distribution ~~in the case of~~for aerosols of a solid or liquid chemical substance and would be determined based on droplet size data for the material and/or liquid application method (*e.g.*, spray, aerosol, mist).

EPA's Functional Group (FG) and Functional Group Equivalent Weight (FGEW) criteria for E1 polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of HMW polymers. Therefore, we propose using these criteria as an initial screen for determining whether a HMW polymer is considered non-reactive and included or reactive and ~~included or~~

> **Commented [ST4]:** There were previous edits from EPA, but not Annie. This seems awkward to me. I think the original text was clearer. Thoughts?
>
> Another option is: "respirable particles that are greater than or equal to 1% by weight (wt%) based on particle size distribution data for the material is the practical inclusion cutoff for assessing respirable particles and is the same cutoff EPA applies to the nonreportable content of nanoscale materials"
>
> **Commented [SS5]:** I prefer the wording in the comment above.

excluded from the category, respectively. As shown in [ REF _Ref46665925 \h \*
MERGEFORMAT ], the E1 polymer exemption criteria include low-concern, moderate-concern,
or high-concern FGs. A summary of rRepresentative FGs meeting each of these hazard concern
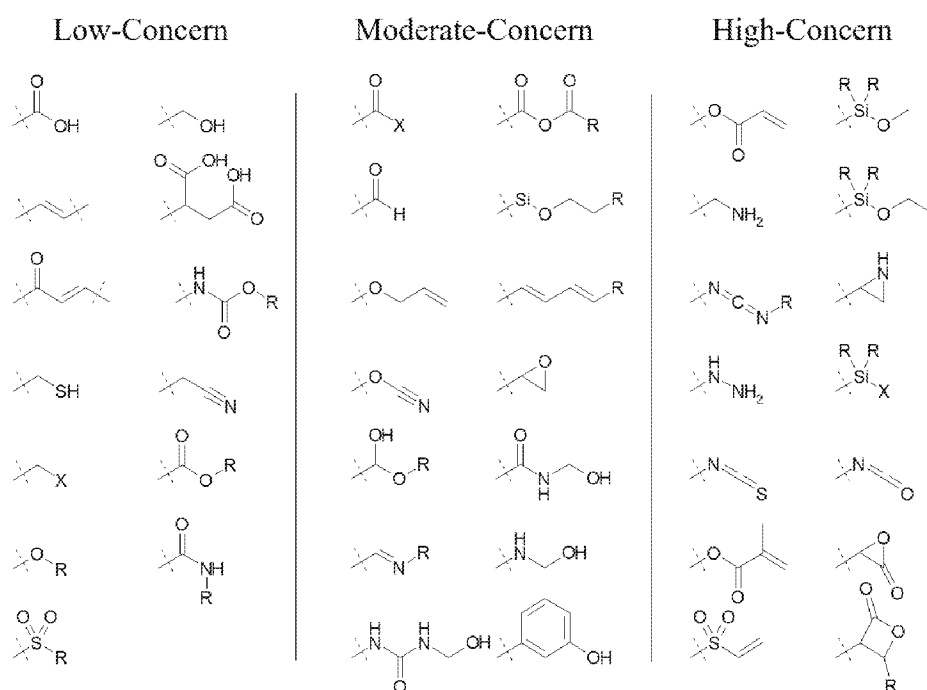levels is shown in [ REF _Ref46674358 \h \* MERGEFORMAT ].

## Low-Concern    Moderate-Concern    High-Concern



**Figure [ SEQ Figure \* ARABIC ].** FG hazard concern levels for polymeric substances meeting
EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for
identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern)
for the HMW polymer category. The following cutoffs are proposed as the category boundaries
for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-

concern FGs (FGEW $\geq$ 1,000), or high-concern FGs (FGEW $\geq$ 5,000). "R" represents an undefined structure; "X" represents a halide. See: EPA (1997) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><Dis playText>[7]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>P olymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] for further details.

A ~~generally recognized~~ property of respirable, low reactive (*i.e.*, low toxicity) particles that ~~can~~ may cause lung overload is the poorly soluble nature of these compounds. EPA has published general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L), slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (> 1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><Dis playText>[30]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key

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type><contributors><authors><author>EPA</author></authors></contributors><titles><title>S

ection 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM,

Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution

Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW,

Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution

Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW,

Washington, DC 20460</full-title></periodical><pages>22,

https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-

748-B12-

001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

These values were not established for evaluating the solubility of particles for lung overload;

however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [

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<EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><D

isplayText>[31]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key

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>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline

for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for

Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-

ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-

chemical-

properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls

></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW

polymers. ECETOC (2013) [ ADDIN EN.CITE

<EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><

DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key

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type><contributors><authors><author>ECETOC</author></authors></contributors><titles><tit

le>Poorly Soluble Particles / Lung Overload</title></titles><pages>130,

http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No.

122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre

for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical

Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-

content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-

Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial

biosolubility screening approach that provided qualitative determinants (*i.e.*, "soluble",

"insoluble", "Low dissolution rate", or "Very high dissolution rate") for assessing biosolubility;

however, no quantitative thresholds were provided. In comparison, the International Commission

on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and

Health (FIOSH) provided quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day$^{-1}$), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day$^{-1}$), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day$^{-1}$) [

ADDIN EN.CITE

<EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">1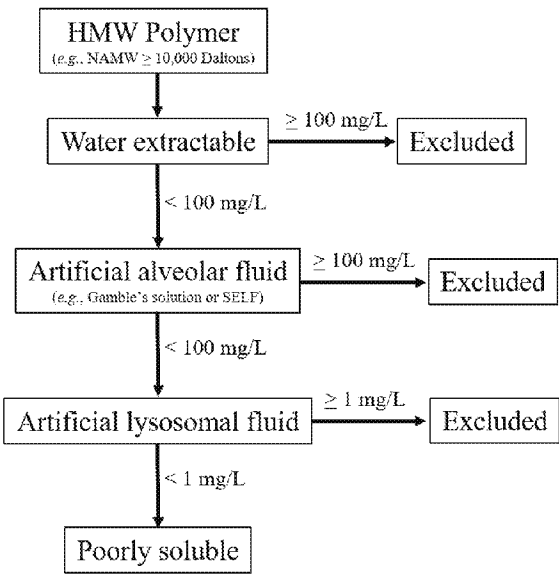7</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title> Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract

Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)&#xD;0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of $\leq 1$ mg/L in artificial lung fluids for identifying particles as "low soluble dusts" [ ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[33]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed ~~previously~~above, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are $\leq 10$ µm and $\geq 1$ wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW

polymer. However, determining whether a HMW polymer is "poorly soluble" and a potential

hazard concern for lung overload is also dependent on the potential daily exposure estimates.

Therefore, we propose using the inclusion/exclusion cutoffs shown in [ REF _Ref46673847 \h

\* MERGEFORMAT ], which consider water extractability/ or biosolubility and the legally

binding permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and

Health Administration (OSHA) for respirable particulates not otherwise regulated or (PNOR)

(*i.e.*, 5 mg/m$^3$).


**Scheme [ SEQ Scheme \* ARABIC ].** Screening criteria for determining water extractability
and biosolubility.

The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first ~~screen~~ step is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been ~~established to correlate~~correlated with either biosolubility or biopersistence. Therefore, EPA's cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected ~~rather than the low water solubility cutoff~~, since it ~~represents a transition from slight to moderate water solubility and~~ is ~~therefore~~ expected to be conservatively inclusive ~~in the first step because water extractability is generally expected~~and to overestimate the insolubility of polymers in biological fluids. In the second ~~screen~~step, ~~two~~biosolubility cutoffs ~~may be used,~~are either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the OSHA PNOR PEL of 5 mg/m$^3$ (*i.e.*, 50 mg/day; 5 mg/m$^3$ × 10 m$^3$/day) for the respirable fraction, defined based on size selective characteristics as particles smaller than 10 μm aerodynamic diameter. The ~~first value is based on EPA (2020) where the Agency applied a~~biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid ~~. This value would~~equates to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ ADDIN EN.CITE

<EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum>< DisplayText>[34]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-